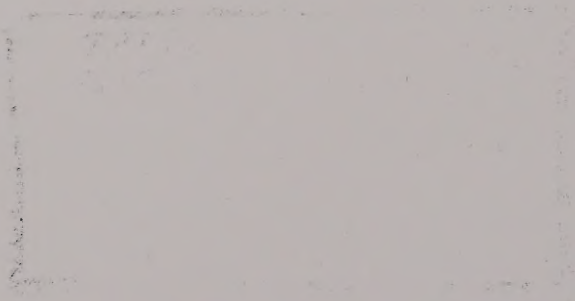
GENE THERAPY ADVISORY COMMITTEE

FOURTEENTH ANNUAL REPORT

Covering the period from January 2007 to December 2007

Health Departments of the United Kingdom
2008



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The GTAC Secretariat may be contacted at:

Department of Health
Area 603, Wellington House
133-155 Waterloo Road
London SE1 8UG

Tel: 0207 972 4351
Fax: 0207 972 4300
Email: gtac@dh.gsi.gov.uk
Website: www.advisorybodies.doh.gov.uk/genetics/gtac/

1.2.2 HIV

GTAC 131: A phase I/II trial to compare the immunogenicity and safety of 3 DNA C prime followed by 1 NYVAC C boost to 2 DNA C prime followed by 2 NYVAC C boost

GTAC 135: A randomised double blind placebo controlled study to evaluate the safety and immunogenicity of a candidate HIV-1 vaccine, MVA.RENTA, delivered intradermally by needle injection, alone or in combination with MVA.HIVA, to HIV-1 seropositive adult subjects receiving Highly Active Antiretroviral Therapy (HAART)

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1.2.3 Malaria

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1.4.1 Heart Failure

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FOREWORD

Welcome to the Fourteenth Annual Report of the Gene Therapy Advisory Committee (GTAC), which covers the Committee's work from January 2007 to December 2007.

The year 2007 has proved to be another productive one for GTAC, with a total of 17 trials reviewed by the Committee. We were also involved in six consultations, one of which was of particular importance to the Committee: a consultation on the proposed changes to the Clinical Trials Regulations. This proposal involved changing the statutory requirement in the United Kingdom for GTAC to review all gene therapy clinical trials. The net outcome, adopted into law in 2008, means that GTAC can now transfer those gene therapy trials which it deems to be of 'low genetic risk' to one of three other nominated UK Research Ethics Committees. This approach is part of a long-standing commitment by GTAC to de-mystify gene therapy and integrate it safely and ethically into mainstream biomedical research. More specifically, it also means that GTAC will be able to fulfil the Government's 2005 commitment for GTAC to oversee the ethical review of certain clinical trials involving stem cells. The experience that GTAC has developed over the past 15 years in reviewing the ethical issues surrounding complex clinical research such as gene therapy should prove invaluable in converting the promise of stem cell science into real therapies for all our patients. This new challenge is one that is likely to excite and exercise us in equal measure.

Our public day was also a new development for GTAC. For the first time, we ran an education day for high school and college students. The day was a great success, judging from the responses we received from the young adults and their teachers, with one of the highlights being a tour of a local gene therapy laboratory. We thank all those individuals who opened their doors to help us produce such an informative day.

Unfortunately, 2007 was not full of positive developments. Late in the year, we were notified that one of the children in a gene therapy trial at Great Ormond Street Hospital had developed Leukaemia, probably linked to the gene therapy. Thankfully, the affected child has apparently responded well to chemotherapy and our thoughts are with the family. Sadly, this incident was not entirely unexpected, as such an adverse event had already been seen in several children in a similar study in France. Despite these difficulties, it is important to reflect at this stage that this particular gene therapy approach, even with these tragic adverse events, still appears to offer the best treatment option available to children suffering from this disease.

Following a review of the data collected to date from the GTAC flagging project, the Committee met to discuss the future of the project in February. We concluded that the time was right to close the project. Although it is disappointing that the project did not achieve its original objectives, it was the first of its kind in the world and highlighted important issues that must be considered should a similar project be attempted at international level.

As ever, our external reviewers, both in the UK and abroad, deserve an extra special thank you for continuing to give up their time and expertise to help ensure that gene therapy in the United Kingdom continues to be conducted to the highest standards of ethics and safety. I must also express my heartfelt thanks to my colleague, and the Vice-Chair of

GTAC, David Harrison, who 'stepped into the breach' on a number of occasions to chair Committee meetings in my absence over the last year. I consider it one of the greatest strengths of GTAC that its members have consistently shown such dedication and commitment to our vital role in gene therapy research.

I hope you will find this report of interest.

Professor Martin Gore
Chairman of GTAC

SUMMARY

In 2007, the Committee considered 17 applications to conduct a gene therapy clinical trial in the UK under its remit as the National Research Ethics Committee for gene therapy clinical research. Unlike in previous years, in 2007 the majority of protocols seen by the Committee were for infectious disease (ten, 59%). Cancer, which in other years has been the front runner, made up only 18% (three) of all trials brought to the Committee.

Since its inception in 1993, the Committee has considered 155 applications, with 126 trials going ahead. Of these, 72 are closed for recruitment and a further 54 are open for recruitment. The remaining 29 trials were either declined by the Committee or never recruited patients because they were withdrawn following initial GTAC approval. Short summaries of some of the closed trials are given in Section 4.

This year was a busy year for the Committee's consideration of regulatory issues. GTAC replied to five public consultations, including two from the European Medicines Agency (EMEA): on non-clinical studies required before the first clinical use of a gene therapy medicinal product; and on a concept paper regarding the development of a guideline for clinical monitoring and follow-up of patients exposed to gene therapy/gene transfer medicinal products. GTAC also responded to a consultation from the MHRA on its proposals for amendments to the Clinical Trials Regulations which will impact on the Committee in the future. The Committee, along with the Department of Health, also took the decision to close the joint GTAC/DH long-term monitoring initiative (the flagging project).

For the public meeting this year, the Committee held an 'education day' for 16- to 18-year-olds, which attracted around 150 young adults and received good feedback. For more information please see Section 3.

The final section of this report details GTAC's terms of reference and membership, external expert advisers, and the summary of UK trials 1993-2007. Around 1,663 patients were enrolled onto UK gene therapy trials by December 2007.

SECTION 1: PROTOCOLS REVIEWED BY GTAC IN 2007

In 2007, GTAC received 17 new applications (GTAC 129 to 145) to undertake gene therapy clinical trials in the NHS. Of these, 11 received full approval and five were conditionally approved. With the remaining protocol, the ethical decision was deferred pending further information. The Committee also considered and approved a sub-study to an ongoing trial (GTAC 124A) and received over 60 applications to amend ongoing protocols.

1.1 CANCER

Cancer is a multi-factorial disease where cells escape the body's control mechanisms and invade, erode and destroy normal tissue. The driving forces in the development of cancer are the cell's genes, which can become damaged by a variety of factors, such as environment, diet and lifestyle. The chance of developing cancer can also be increased by an individual's genetic make-up, such as, in cases of familial breast and ovarian cancer due to mutations in the BRCA and other genes. There are over 200 different types of cancer that can occur anywhere in the body. Surgery is usually the treatment of choice. However, cancer is less amenable to curative surgery once it has spread beyond the original tumour (metastasised). Gene therapy offers a new, but still experimental, potential treatment that could complement conventional treatments such as surgery, chemotherapy and radiotherapy. In fact, approximately 62% of all gene therapy clinical trials in the UK aim to develop treatment for cancer (see Figure 3, Annex G).

1.1.1 Liver Cancer

Hepatoma, which is also known as hepatocellular carcinoma or HCC, is the most common type of primary liver cancer. It accounts for over 85% of all liver cancers. It is more likely to develop in men than in women and becomes more common with increasing age. Liver cancer, in all its forms, is the fifth most common cancer in the world and will kill almost all who develop it within a year. What's more, the frequency of liver cancer is on the rise. This is believed to be primarily due to the increase of chronic hepatitis C (an infection that can lead to liver cancer). Current treatments for liver cancer do not have a high success rate.

GTAC 129: An ascending dose trial of the safety, tolerability and biological effect of intra-arterial injection of the selectively replication competent herpes simplex virus HSV1726 in patients with unresectable hepatocellular carcinoma

Usually the herpes simplex virus causes infections such as coldsores, genital infections and a rare brain infection (encephalitis). HSV1716 is a modified form of this virus which cannot infect cells that are not themselves rapidly dividing. Tumour cells are rapidly dividing and HSV1716 should be able to selectively infect these cells and hopefully kill them (a process called "oncolysis"). In GTAC 129, unlike most other gene therapy vectors considered by GTAC, HSV1716 does not contain a therapeutic gene as such – it is the action of the modified virus itself that is "therapeutic". It was the fifth time the Committee had seen this product. This protocol was discussed in February 2007 when it was given approval.

1.1.2 Solid Organ Cancers

GTAC 139: A phase I open label dose escalating study of the safety tolerability and tumour specific replication of the intravenous administration of green fluorescent protein encoded genetically engineered attenuated vaccinia virus GL-ONC1, with real time imaging in patients with advanced solid organ cancers

This is a novel protocol for patients with advanced-stage, primary or metastatic, solid tumours who have not responded to standard therapy or for which no curative standard therapy exists. This means that patients on this trial will be critically ill (a life expectancy of at least three months). They will also be diverse in terms of their cancer (solid cancers are defined as abnormal cellular growths in "solid" organs such as the breast, prostate, pancreas, ovaries, liver, kidney, lung, etc – as opposed to leukaemia, a cancer affecting the blood, which is a "liquid" cancer).

The strategy employed in this study is to use an oncolytic virus based on vaccinia virus which selectively infects dividing cells such as tumour cells (but not limited to tumour cells). By infecting the cell, the virus destroys the (cancer) cell. The word oncolytic is composed of "onco" for cancer and "lytic" for destroy (or lyse). In addition to this anti-cancer activity of the modified vaccinia virus itself, the product used in this study also carries three "marker" genes – which are not therapeutic but help assess where in the body the gene therapy virus has gone. This protocol was discussed in October 2007 when it was given GTAC approval.

1.1.3 Colorectal Cancer

Colorectal or bowel cancer is cancer of the colon or rectum. It is the third most common form of cancer and the second leading cause of cancer-related deaths in the West, causing some 655,000 deaths per year worldwide. The cancer is usually asymptomatic until it has reached an advanced stage. This is why some organisations advocate regular screening for those in the high-risk category. As with all cancers, the earlier it is caught the greater the chance of cure.

Colorectal cancer begins as adenomas (a group of growths) that resemble a polyp. Colon polyps are fleshy growths that occur on the inside (the lining) of the large intestine, also known as the colon. Colon polyps develop when chromosome damage occurs in cells of the inner lining of the colon. When certain types of polyps grow large enough, they can become cancerous. Therefore, removing benign colon polyps can prevent colorectal cancer. Initially, however, most polyps are benign and experts believe it takes around 5 years for these growths to become malignant. Treatment is very much dependent on when the cancer is found; it generally involves surgery followed by chemotherapy and occasionally radiotherapy (either before or after the surgery).

GTAC 141: QUASAR V: A multi centre randomised placebo controlled trial of TroVax® vaccination in the adjuvant treatment of stage II and stage III colorectal cancer

The product TroVax is well known to GTAC. It is based on a highly attenuated Modified Vaccinia Ankara (MVA) virus and contains the gene for a human glycoprotein called oncofetal antigen (or 5T4). 5T4 is found on the surface of many cancer cells. As with most cancer gene therapy approaches, the strategy here is "immunotherapy", which informs the

immune system of the presence of the cancer cells (i.e. those that have 5T4 on their surface) so that the immune system of the patient can target and kill the cancer cell. The protocol was discussed by GTAC in October 2007 and was conditionally approved.

1.1.4 Renal Cancer

GTAC 124A: TRIST-IR – Analysis of immune responses in a sub-set of patients enrolled into an international, randomised, double blind, placebo controlled, parallel group study to investigate whether TroVax® added to first-line standard of care therapy, prolongs the survival of patients with locally advanced or metastatic clear cell renal adenocarcinoma

This study is a sub-study of GTAC 124, which was approved in 2006. It is not a clinical trial, but rather an application to collect extra blood samples over and above those donated on the main study in order to investigate whether immune responses to the study product (and therefore the cancer) mounted by patients enrolled into the main study relate to the observed clinical responses. This study was discussed by the Committee in October 2007 and given final approval in December 2007.

1.2 INFECTIOUS DISEASE

A disease is classed as infectious if it is the direct result of the presence of pathogenic microbial agents such as bacteria, viruses or parasites. Infectious diseases are contagious, which means that they can be transmitted from one individual to another or even on occasion between species. A topical exmple of this would be influenza: there is widspread concern that 'birdflu' may affect humans. Gene therapy for infectious disease is based upon the creation of a genetic vaccine, which can be based on various different vectors as carriers for the therapeutic gene. The gene usually originates from the pathogen to which a vaccination effect is intented. Its conversion in the body results in the production (called "expression") of a foreign protein (called an "antigen") which, it is hoped, may trigger the body to mount an immune attack against the protein – and ultimately against the pathogen. It is hoped that by utilising the benefits of gene therapy it will be possible to prevent infection and create 'cures' for diseases, such as HIV, for which currently none exist. In 2007, gene therapy for infectious disease made up a large proportion of all trials seen.

1.2.1 Tuberculosis

Tuberculosis (TB) is an airborne infectious disease which usually, but not always, affects the lungs. Typical symptoms include fever, night sweats and coughing up blood. It is spread when a person with active TB disease of the throat or lungs coughs or sneezes and those in close proximity breathe in the bacteria and themselves become infected.

GTAC 130: A phase I study to assess the safety and immunogenicity of new TB vaccine candidates FP85A and MVA85A in healthy adults who have previously been immunized with BCG, using a prime boost delivery schedule

GTAC 134: Measurement of human T-cell turnover following vaccination with the tuberculosis vaccine MVA85A

GTAC 137: A randomised open labelled phase II non inferiority clinical study between two manufacturing process for the tuberculosis vaccine MVA85A

All three of these trials are looking into studying the effect of a candidate vaccine called "MVA85A", which is based on Modified Vaccinia Ankara virus and carries as the gene load a sequence from *Mycobacterium Tuberculosis (M.tb)* antigen 85A. The antigen is highly conserved in all mycobacteria species, and is a major secreted antigen from *M.tb.*

GTAC 130 is a study which investigates two possible TB vaccines, MVA85A and FP85A, for a recombinant Fowlpox virus carrying the same gene load. The objective of this trial is to assess the safety of FP85A when administered individually and sequentially with MVA85A in a prime-boost regime to healthy volunteers who have previously been vaccinated with BCG. This application was given approval when it was discussed in February 2007.

GTAC 134 is a related study designed to measure the rates of proliferation and disappearance of responding immune cells (so-called T-lymphocytes) following vaccination with MVA85A in individuals who have previously received the BCG vaccination. This trial was discussed in April 2007 and was given approval.

GTAC 137 is a study designed to evaluate the original production process for the vaccine alongside a new 'scale-up' manufacturing process. This study was discussed in July 2007 and received approval.

1.2.2 HIV

Human Immunodeficiency Virus (HIV) is a retrovirus, a virus built on RNA rather than the more typical DNA, that causes AIDS (Acquired Immunodeficiency Syndrome). AIDS develops when the immune system cannot control the HIV virus and begins to fail, leading to many different life-threatening illnesses, such as rare cancers, pneumonia and TB. Infection in humans is classed as a worldwide pandemic.

HIV is transmitted person to person by three main routes: unprotected sexual intercourse; contaminated blood products and needles; or transmission from mother to baby at birth or from breast milk. The introduction of combination antiretroviral drugs reduces both the mortality and the morbidity of HIV infection but such drugs are not currently available routinely in all countries. Combination antiretroviral drugs are not a cure but aim to control HIV levels in the blood.

GTAC 131: A phase I/II trial to compare the immunogenicity and safety of 3 DNA C prime followed by 1 NYVAC C boost to 2 DNA C prime followed by 2 NYVAC C boost

This trial utilises the same vaccine as two previous trials, namely GTAC 75 and GTAC 85. This is a study where the vaccine consists of a highly attenuated strain of Vaccinia virus, NYVAC, expressing HIV genes derived from a Clade C HIV-1 strain, which has been shown to be representative of strains circulating in India and China. The vaccine is designed to evoke an immune response in humans against the HIV-1 clade C antigens. When this trial was discussed in February 2007 it was given approval by the Committee.

GTAC 135: A randomised double blind placebo controlled study to evaluate the safety and immunogenicity of a candidate HIV-1 vaccine, MVA.RENTA, delivered intradermally by needle injection, alone or in combination with MVA.HIVA, to HIV-1 seropositive adult subjects receiving Highly Active Antiretroviral Therapy (HAART)

This is a continuation study of GTAC 079: "A pilot study to evaluate the safety, tolerability and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, delivered to HIV-1 seropositive adults receiving HAART". The study uses two gene therapy vectors. The idea with both vectors is that they may stimulate the immune system to mount an immune attack against the HIV virus (immunotherapy) by eliciting a strong T-cell response. Both vectors are based on recombinant Modified Vaccinia Ankara virus and they carry a combination of HIV-derived antigens (immunogens). This trial was given approval when it was discussed by the Committee in July 2007.

GTAC 145: A randomised open labelled Phase II immunogenicity and exploratory efficacy evaluation of therapeutic immunisation +/- IL-2 GM-CSF and growth hormone in HIV-1 infected subjects receiving Highly Active Antiretroviral Therapy (HAART)

This is a study with a HIV clade B plasmid DNA vaccine which contains a number of genes from part of the HIV-1 genome and other epitopes (areas on the virus that draw out the natural immune response) to create a fusion protein. The strategy is based upon the hope that the fusion protein will stimulate patients' immune systems to the presence of the virus. Some volunteers will also receive immunotherapy drugs designed to help the immune system. The Committee gave this application conditional approval when it was discussed in the December 2007 meeting.

1.2.3 Malaria

Malaria is classed as the most important tropical disease today, with somewhere between 300 and 500 million clinical cases worldwide per year. Of these there will be some 1.5-3 million deaths, which puts malaria among the top killers in the world. 90% of cases occur in tropical Sahara regions, although the malarial parasite can be found in around 100 countries. It affects not only those that live in these areas but also travellers to these regions. A vaccine would be most welcome for malarial treatment, not only for those travelling to the areas of the world where there is a risk of infection, but also for those living and working there.

Malaria is spread between humans through the feeding of the female anopheles mosquito. The female mosquito is infected through biting an infected individual; when the mosquito then feeds on another individual, the parasite can be passed on. Within a very short space of time after a human has become infected, the parasite will have made its way to liver cells, which it enters to reproduce; it can also reproduce within red blood cells. By spending time inside cells, it can evade the immune system.

GTAC 133: A phase I study to assess the safety and immunogenicity of a new candidate malaria vaccine, AdCh63 ME-TRAP alone and MVA ME-TRAP using a prime boost delivery schedule

GTAC 142: A phase I study to assess the safety and immunogenicity of a new candiadate malaria vaccine AdCh63 AMA1

The following two studies make use of a new gene therapy vector based upon AdCh63 – Chimpanzee Adenovirus 63. The use of a chimpanzee adenovirus was new to GTAC; indeed, this was the first time an AdCh63 vector was proposed for use in a human clinical trial. The rationale given for using a simian adenovirus is that there is a much lower chance of individuals having prior immunity (hence a reduced immune reaction to the vector when compared with human adenovirus).

GTAC 133 uses two investigational genetic vaccine products: a vector based on the novel recombinant chimpanzee adenovirus 63 (AdCh63 ME-TRAP), and a vector based on recombinant Modified Vaccinia Ankara virus (MVA ME-TRAP). Both vectors carry the genes for multiple epitopes (regions on the surface of the malaria antigen that elicit an immune response) and the malarial parasite protein Thrombospondin Related Adhesion Protein (TRAP). TRAP is a protein thought to facilitate parasite entry into the liver cells (hepatocytes). This study was disucssed by GTAC in May 2007, when it was given conditional approval, and then given full approval by the Committee in June.

GTAC 142 is a related study where the AdCh63 carries the gene for "apical membrane antigen" (AMA1). AMA1 is a protein that is produced on the membrane of *plasmodium falciparum*. It is also highly conserved and it is hoped that this will mean that any immune response to AMA1 will work against many different subgroups of *p. falciparum*. This application was seen by the Committee at its October 2007 meeting and it was decided that there was not yet enough supporting information available to give an ethical opinion

1.2.4 Influenza

Each winter, the Influenza virus kills around 4,000 people in the UK, with the world total at between 500,000 and 1 million generally spreading throughout the world in a seasonal epidemic. Influenza virus affects mainly the upper respiratory tract (nose, throat and bronchi but rarely the lungs) and the individual remains infectious for about a week. It is an infectious disease of birds (such as the H5N1 strain) and mammals.

GTAC 143: A phase I study to assess the safety and immunogenicity of a new influenza vaccine candidate MVA-NP+M1 in healthy adults

This study uses a recombinant Modified Vaccinia Ankara virus (MVA), which carries 2 genes fused together: the gene for nucleoprotein (NP) from H3N2 (it is necessary for virus replication), and the matrix protein (MP1, a protein that lines the inside of the outer lipoprotein envelope of the influenza virus). This trial was given approval by the Committee in December 2007.

1.2.5 Hepatitis C

Hepatitis (inflammation of the liver) can be caused by a variety of different reasons, from drug or alcohol inducement to viral hepatitis. Hepatitis C is one of about seven other identified viral hepatises. It is estimated that between 150 and 200 million people worldwide are infected with Hep C and of those around 200,000 are thought to be living in England. As

the infection is largely asymptomatic, accurate numbers are difficult to determine. Many do not know they are infected until the infection reaches the chronic phase.

Infection by Hep C (or indeed any form of hepatitis) damages liver function, which can cause liver cancer and liver damage which can lead to cirrhosis of the liver (very severe liver damage) and perhaps the necessity for a liver transplant. Of those who are infected, around 25% will naturally clear the infection. The remainder will go on to the chronic phase of infection. Of these the majority will lead normal lives with a normal life span. About 20% of all people infected with Hep C will go on to develop cirrhosis.

GTAC 144: A phase I study to assess the safety and immunogenicity of new Hepatitis C virus vaccine candidates AdCh3NSmut and Ad6Nsmut

In this study there are two new candidate vaccines. Both are replication incompetent adenoviruses. The first is based on Ad6 (Human adenovirus 6), the other is based on AdCh3 (Chimpanzee Adenovirus 3), which has not been used in human clinical trials before (a so-called first-in-human application). Both viral vectors carry multiple antigens from the Hepatitis C virus in the hope that their production in the body via the gene therapy may stimulate the body's defences against Hep C infection. In December 2007 the Committee gave conditional approval to this application.

1.3 SINGLE GENE DISORDERS

Much like the name suggests, single gene disorders are conditions which are the direct result of a mutation in a single gene. There are about 6,000 known single gene disorders, ranging from primary immunodeficiencies (such as X–SCID below) to sickle cell anaemia, Huntingdon's disease, Haemophilia or Fragile X syndrome. Single gene disorders occur in around 1 in 200 births, but due to their nature can often be predicted. Single gene disorders generally follow one of a few inheritance patterns: autosomal dominant (where only one copy of the mutated gene is required for an individual to be affected); autosomal recessive (where two copies are required for an individual to be affected; individuals with only one copy are known as 'carriers'); X linked dominant (as the name suggests, the mutation is found on the X chromosome; these mutations are quite rare); X linked recessive (also found on the X chromosome, therefore affecting far more males than females and more common than X linked dominant conditions); Y linked (which only affect males, as the mutation is found on the Y chromosome alone); and Mitochondrial disease (which is also known as maternal inheritance, as only egg mitochondria are found in the developing embryo).

GTAC 132: Gene therapy for SCID-X1 using a self inactivating (SIN) gammaretroviral vector

X-linked SCID is an inherited disorder that affects boys, rendering them extremely susceptible to infections such as from bacteria and viruses. These children can be isolated in sterile environments for a short period of time and can also be given drugs to protect against infection whilst waiting for a bone marrow transplant (BMT). If not treated, boys with SCID normally die before they are 1 year old. In X-SCID babies, the immune system is not effective because certain types of specialised blood cells (lymphocytes), whose normal function is to fight infections, fail to develop properly. In X-SCID the lymphocytes lack on their cell surface a functional protein (encoded by the gamma-c gene) which would normally receive signals from

molecules called "cytokines". The correct reception and processing of these signals is essential if the cells are to develop properly into fully functional and "mature" lymphoctes.

This new gene therapy study builds on the previous X-SCID trial, which closed in 2006 (GTAC 045). It uses a new and improved vector based on a gammaretrovirus with a self-inactivating (SIN) configuration. This means that expression (production in the body) of the therapeutic gene is regulated by an internal housekeeping human gene promoter. In theory, the vector should have a greater safety profile but this has not yet been tested in humans. The features are anticipated to reduce risks of insertional mutagenesis (gene disruption) while retaining efficacy. The therapeutic gene is, as before, a healthy copy of the human common cytokine receptor gamma-c chain, which is defective in X-SCID boys. During discussions the Committee invited Dr Andrew Gennery to present his data on bone marrow transplants in Newcastle and is grateful for his help and assistance in helping to set the context for this study. The Committee gave approval for this trial in May 2007.

GTAC 140: Safety evaluation of a single escalating dose of pGM169/GL67A in the nose and lung of individuals with Cystic Fibrosis

Cystic Fibrosis (CF) currently affects about 7,500 people in the UK. It is the most commonly inherited disease in the UK. CF develops due to mutations in the gene for a protein called "Cystic Fibrosis Transmembrane Conductance Regulator" (CFTR). CFTR is produced on the surface of epithelial cells (these cover internal and external surfaces of the body, including the lining of vessels and other small cavities), and it has many functions, the most important of which is thought to be ion transport.

This gene therapy study uses a plasmid vector which carries a healthy copy of the CFTR gene mixed with a lipid called GL67. Because plasmid DNA is negatively charged and the lipid is positively charged, the two components "attract" each other. This results in a shrinking (called condensation) of the combined particles by comparison to the plasmid alone, which is very large. The size, and charge, of a particle largely determines its chances to be taken up by cells in the body. Approval for this study was given in October 2007.

1.4 CARDIOVASCULAR DISEASE

Cardiovascular disease is the name given to a wide range of different conditions that affect the heart and/or blood vessels. Examples would include coronary artery disease, stroke, and heart failure. It is the biggest killer in the world today and in Britain one person in three may die from cardiovascular disease (or heart disease). Cardiovascular disease can be acquired through certain behaviours such as smoking, a lack of exercise or a poor diet but it can also be caused through genetic familial factors.

1.4.1 Heart Failure

GTAC 136: Investigation of the safety and feasibility of SERCA gene transfer in the human failing heart using an adeno-associated viral vector

Heart failure is a condition resulting from any structural or functional cardiac disorder which impairs the ability of the heart to fill or pump enough blood around the body to satisfy bodily needs. It is not the same as cardiac arrest, which is the termination of normal

heart function which can ultimately lead to death. Worldwide there are more than 500,000 new cases of heart failure each year and even with the best treatments, heart failure carries a yearly mortality rate of around 10%. There are many different causes for heart failure, including stress, smoking, old age (heart failure often occurs in the over 65s) and obesity. There is also the possibility of genetic family history of heart failure where there are thinner heart muscle walls, leading to a weak heart.

The gene therapy vector used in this study is based on AAV6 (adeno-associated virus, serotype 6), which has a good safety record and tropism for the heart muscle. The therapeutic gene is "sarcoplasmic reticulum calcium ion adenosine tri-phosphatase 2a (ATPase 2a)" or SERCA2a. SERCA2a is an energy pump and the amount of calcium it stores determines the intensity of the heart pump. For those with heart failure the pump is poor due to low amounts of SERCA2a and thus a lower calcium store. It is hoped that increasing the amount of SERCA2a (and calcium held) will increase the power of the heart contraction. This study was given approval by the Committee in July 2007.

1.4.2 Peripheral Artery Disease

GTAC 138: A randomised double blind placebo controlled parallel group study of the efficacy and safety of 4 administrations of XRP0038/NV1FGF 4mg at 2 week intervals on amputation or any death in critical limb ischemia patients with skin lesions.

Critical Limb Ischemia (CLI) is a severe obstruction of fat-like deposits of the arteries which critically lowers blood flow to the extremities of the body. It can be associated with individuals with severe Peripheral Arterial Disease (PAD), hypertension, hypercholesterolemia, smoking and diabetes. It is generally an older person's disease. However, in those with diabetes it often develops at a much younger age. Critical Limb Ischemia is typically characterised with foot pain at rest (usually described by patients as a burning pain in the arch, ball or toes of the foot), and non-healing wounds and gangrene (both from the lack of blood supply to the limb). It can also be measured as impaired blood flow through the obstructed arteries.

The gene therapy product used in this study is called XRP0038/NV1FGF. It is a plasmid encoding the gene for FGF-1, the human acidic fibroblast growth factor which promotes the stimulation of "angiogenesis" in the affected limbs by cell growth and migration. Angiogenesis (new vessel growths) is the physiological process where there is growth of new blood vessels from ones that already exist. For instance, as patients with CLI will be experiencing wounds on their extremities that will not heal due to poor blood supply, it is hoped that FGF-1 mediated angiogenesis may help with pain as well as increasing general blood supply to the limb. The Committee gave approval to this study in October 2007.

1.5 AMENDMENTS TO ONGOING PROTOCOLS

In 2007, GTAC processed 12 applications for approval of substantial amendments at Committee meetings, including several trials for which approvals were revalidated (as more than 24 months had lapsed between the initial approval by GTAC and the proposed commencement of the study following all regulatory approvals), and over 50 applications for approval of substantial amendments between Committee meetings.

SECTION 2: REGULATORY AND GUIDANCE ISSUES

2.1 CLOSURE OF THE LONG-TERM MONITORING PROJECT ('THE FLAGGING PROJECT')

In 1999/2000, GTAC/DH initiated a research study called "the long-term monitoring of patients participating in gene therapy." In 2007, GTAC/DH conducted a review of the "flagging project". GTAC, in consulation with a range of experts, decided to close the project at its Committee meeting in February 2007. A note of the discussion that took place is appended in Annex F. For further information on the now closed flagging project, please see the GTAC website at www.advisorybodies.doh.gov.uk/genetics/gtac/flagging.htm

2.2 PUBLIC CONSULTATIONS CONSIDERED

In 2007, GTAC discussed and commented on five consultations from a variety of sources.

2.2.1 *Draft ABPI guidelines for phase I clinical trials*

This consultation, run by the ABPI (Association of the British Pharmaceutical Industry), was discussed by GTAC during its May meeting. In particular, the Committee considered and commented on the section concerned with compensation and how to appropriately set compensation levels as well as more general issues such as approval times for trials and the GTAC process.

2.2.2 *Update to the Code of Practice for Scientific Advisory Committees*

During 2007, the Office of Science and Innovation (now called Government Office for Science) consulted on an update of its Code of Practice for Scientific Advisory Bodies, which affects GTAC in its role as a Ministerial Scientific Advisory Body. Though there were specific questions that the Committee replied to, much of the discussion members had on the document during the discussion at the July meeting related to the term 'lay' member and the classification used.

2.2.3 *EMEA guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products*

GTAC was invited in September 2007 to comment on the above EMEA consultation. The Committee was broadly content with this and had no substantial comments.

2.2.4 *The development of a guideline for the clinical monitoring and follow-up of patients exposed to gene therapy/gene transfer medicinal products*

During 2007, the EMEA produced a concept paper on the development of a guideline on clinical monitoring and follow-up of patients exposed to gene therapy/gene transfer medicinal products. The Committee responded to this consultation in light of the GTAC/DH flagging project, which had recently closed, explaining some of the practical difficulties that GTAC had encountered. GTAC commented on the UK position that the majority of gene therapy patients are already followed for life, in particular in cancer trials where patients are critically

ill and time of survival is often a trial endpoint. In terms of the paediatric population, due to the nature of their disease these individuals are already under regular clinical surveillance. GTAC also commented on the objective of a follow-up initiative, and whether it will be the intent to monitor the safety of individual patients or rather to draw conclusions about the safety of certain gene therapy products more generally. The Committee proposed questions which must be considered in either case, including the possible need for a control group to be required for valuable data to be generated.

2.2.5 Challenges and Priorities for the MHRA

During the October 2007 meeting, the Committee discussed a consultation document from the MHRA on future challenges and priorities that the Agency expects to face in the next five years. The Committee took this opportunity to conduct its own horizon scanning to feed into the MHRA consultation about where GTAC expects gene therapy research to go in the future.

2.2.6 Changes to the Clinical Trials Regulations

During the October 2007 meeting, the Committee considered a MHRA consultation document which outlined plans to amend the Clinical Trials Regulations. There were three proposed changes to the regulations:

- To allow trials of emergency care medicines on children without initial consent
- To provide greater flexibility in the operation of ethics committees and their appointing authority
- To clarify which trials require ethical review by GTAC

The Committee discussed these proposed amendments at length at its October 2007 meeting, in particular the amendements relating to GTAC's function under the Regulations, and provided a detailed response to the consulation.

2.3 CONSIDERATIONS OF AN ADVERSE EVENT IN THE X-SCID GENE THERAPY TRIAL (GTAC 045: PHASE I CLINICAL GENE THERAPY PROTOCOL FOR X-LINKED SEVERE COMBINED IMMUNODEFICIENCY)

In December 2007, the Committee was informed that one of the children in the UK X-SCID trial, at Great Ormond Street Hospital in London, had developed T-cell leukaemia. This trial has been closed since the previous year (2006) but all participating children are in regular clinical follow-up and care. The risk of leukaemia in X-SCID trials had already been documented in France, where 4 of 11 children had also developed leukaemia as a result of the gene therapy. The Committee discussed this news at length and was in regular contact with the investigators, who kept the Committee informed of new information coming to light.

For further information on the case please see the Great Ormond Street Hopspital website (www.ich.ucl.ac.uk/pressoffice/). The reader may also be interested in the information published on the website of the European Society for Gene and Cell therapy, which includes a commentary from the Board on this event (www.esgct.org/newsletter.cfm).

SECTION 3: GTAC PUBLIC MEETING – GTAC EDUCATION DAY

GTAC's 2007 public meeting was a first for the Committee. Rather than targeting interested individuals, the Committee ran a 'school day' targeted at young adults aged between 16 and 18. There was a total of seven schools that signed up for the day, bringing a total of around 150 young adults. The morning was spent with 10 different speakers, each giving a presentation on their area of expertise. In the afternoon, each school group was given the opportunity to visit a working gene therapy laboratory in a London University.

3.1 SUMMARY

The day was chaired by Professor David Harrison and was opened with a welcome by Professor David Latchman, Master of Birkbeck College. The first talk of the day was given by GTAC member Professor Mary Collins, who gave a brief introduction to gene therapy, including information on different types of vectors and how gene therapy works.

The second session was a 'gene therapy showcase' where four researchers gave brief, 10-minute presentations on their gene therapy research. The first was Professor Robin Ali, who discussed gene therapy for retinal degeneration. He was followed by Dr Rachel Midgley, who presented on cancer gene therapy. The third presentation was on gene therapy for Cystic Fibrosis, given by Professor Eric Alton. The final presentation in this session was by Professor Andy Baker, another GTAC member, who discussed gene therapy for cardiovascular disease.

The final session featured three GTAC members: Professor Richard Ashcroft, who discussed the ethical and social considerations of gene therapy, followed by Mrs Debbie Beirne, who invited those assembled to think about consent issues, and finally, Professor David Harrison, who commented on the possible future of gene therapy. After the presentations there was an opportunity to question each of the speakers, which gave rise to some lively debate.

3.2 WHAT THE AUDIENCE THOUGHT OF THE PUBLIC MEETING

GTAC received excellent feedback from the event, with 128 feedback forms being handed in. Delegates rated the event overall as Excellent (33%) or Good (52%), giving an overall 85% positive rating. Most delegates rated the speakers as Excellent (27%) or Good (55%), with an overall positive rating of 82%. The question and answer session was rated Excellent (22%) or Good (42%), and the delegate pack was rated Excellent (34%), Good (40%) or unrated (29%). The promotional flyer was rated Excellent (46%) or Good (25%).

Best of all, a very positive 78% of delegates stated the event had helped with their studies and an equally high 72% said that the event had changed their perception of gene therapy.

Thank you to all our speakers on the day and in particular to Professor David Harrison for chairing the meeting.

SECTION 4: UPDATE OF CLOSED UK CLINICAL TRIALS

The following are short summaries provided by researchers of closed gene therapy trials. GTAC would like to thank all researchers who have contributed to this section, which builds on initiatives of the 2004, 2005 and 2006 reports. The summaries are essentially unedited and reflect the views of the researchers.

4.1 GENE THERAPY FOR INFECTIOUS DISEASE

GTAC 085: A Phase I trial to compare the safety and immunogenicity of HIV DNA-C prime-NYVAC-C boost to NYVAC-C alone

The EV02 study was an early safety study (Phase I) in which 40 healthy volunteers were randomly enrolled to one of two groups. One group received 2 x DNA C priming immunisations followed by 2 x NYVAC C boost immunisations, and the other group received the NYVAC only. The NYVAC is based on the vaccinia (pox) virus, which was used as a vaccine in the prevention of smallpox. The part like vaccinia is called NYVAC and this acts as a carrier for the genetic code for certain HIV proteins that we hope will produce a broad immunity to HIV. The DNA HIV-C consists of two plasmids (pieces of DNA), together representing the genetic code that is inserted into the NYVAC described above. This was the first study of this DNA product. There was considerable care to remove proteins that could be associated with side effects. The main aim of the study was to assess the safety and immune responses of the prime boost regimen (DNA C + NYVAC C) and to compare these to the single agent (NYVAC C) in healthy volunteers at low risk of HIV infection.

Safety data were collected on events that are recognised to be associated with vaccines prior to immunisation, one hour after the intramuscular injection, and at least once within the week following the intramuscular injection. Participants were asked to complete diary cards describing the same solicited events on a daily basis for seven days following immunisation, or longer if events were ongoing. Data on other clinical events and laboratory events were collected with an open question at each visit and through routine scheduled investigations respectively.

Immune responses were measured in a single laboratory using the "interferon-gamma ELISpot" assay, which is a standard international test to assess cellular responses.

Study Population

Twenty three volunteers were randomised to receive DNA C followed by NYVAC C and 17 were randomised to receive NYVAC C only. Three subjects in the DNA C/NYVAC C group prematurely discontinued vaccinations; two because of adverse events after the first DNA C vaccinations and one withdrew consent after the second DNA C vaccination. Two subjects in the NYVAC C only group were lost to follow-up prior to receiving the NYVAC C vaccinations.

Safety Results

Two subjects were withdrawn from the study due to adverse events. One had abnormal liver chemistry picked up on screening, which settled before enrolment. Immediately after the first DNA vaccine the liver chemistry was abnormal again, and worse than during screening. Although he was well throughout and the abnormality settled within 10 days, it was considered in his best interests to stop further injections. The second subject experienced a moderately severe faint after the first DNA injection and again, the doctors thought that it was better not to proceed with further injections. Otherwise the DNA immunisations were well tolerated, as were the 2 NYVAC immunisations. Adverse events were consistent with those seen following licensed vaccines. This increases confidence in the procedures to make vaccines made through genetic modification safe.

Immune responses

These were higher than expected, with 90% (18 of 20) of volunteers that completed the prime boost immunisations responding. This was compared with 33% (5 of 15) that received NYVAC alone, which was significantly worse, suggesting that the DNA played an important role. The majority of these responses were to the proteins on the envelope of HIV.

In previous studies, DNA had not performed well. The scientists believe that the higher concentration of DNA (4mg per ml) used in this study is the most likely explanation, and this was an important lesson for the field.

Next steps

These results have informed the next study, which is being undertaken in a larger group of 140 volunteers. This is through a collaboration between EuroVacc and the French ANRS. There are two groups being studied: one is receiving 3 x DNA C prime followed by 1 x NYVAC C and the other is receiving the 2 x DNA C and 2 x NYVAC C described above. It is anticipated that the third DNA will improve the immune responses so that there are more responses to the core proteins of HIV as well as the envelope.

4.2 CANCER GENE THERAPY TRIALS

GTAC 084: A Phase I Study of Immunotherapy for Patients with Metastatic Melanoma using Dendritic Cells Transfected with Plasmid Encoding Two Melanoma Antigens

The present treatment

The use of dacarbazine chemotherapy, and of cytokines, interferon and interleukin treatment are each associated with a 5-20% response rate. There is a need for better treatment options to be developed.

The use of Dendritic cells (DCs)

T cells are white blood cells that survey all cells in the body and can recognise a cell making particular proteins. A protein recognised by a T cell is called an antigen. This part of the immune system evolved to kill virus-infected cells that are making foreign proteins. For more than two centuries, humans have injected weakened viruses to artificially educate T

cell immunity to recognise foreign proteins and thereby prevent life-threatening infections. It is now recognised that another group of immune cells plays a key role in presenting an antigen to T cells and in determining whether or not a specific T cell response will be activated. These immune-activating cells are called dendritic cells.

The trial

The purpose of this trial is to educate the T cells in patients with malignant melanoma to recognise two proteins that might lead to selective killing of the malignant cells. Antigens are molecules that can be targets for the immune system. Gp100 and MART 1 are antigens that are made only in normal pigmented cells called melanocytes and are often over-abundant in malignant melanoma cells. Successful vaccination might result in killing of normal melanocytes as well as cancer cells.

Non viral method

Weakened viruses have been used experimentally to vaccinate against cancer, just as they have been used to prevent infectious diseases. Genes that code for antigens are engineered into the virus – the virus is then called a "vector". However, in this trial we used a novel non-viral gene delivery system that efficiently transfects human dendritic cells. A non-viral delivery system has a number of advantages over viral vectors. The immune system can make a response against a viral vector that can dominate over the desired immune response against the TAA. This is less likely with a non-viral system. There are fewer regulatory and safety concerns about using a non-infectious non-viral vector. A chemical rather than a living vector can be manufactured more easily, more safely and more reproducibly.

Objectives of Study

Primary

- To determine the safety and tolerability of the cutaneous administration of autologous transfected dendritic cells expressing MART-1 and gp100

Secondary

- To determine clinical responses
- To determine T cell responses

Methods

- Non-randomised open-label phase I / II trial
- Single-dose level of transfected DC – up to 5 x 10^6 DC
- Vaccination in 2-4 divided doses given near lymph nodes not involved by disease and by both intra-dermal and sub-cutaneous routes

Results

27 patients gave consent, 24 received at least cycle 1, and 22 were evaluable for response

Adverse Events

- Local injection site reactions
- Overall, there was minimal injection-site toxicity – this affected 15/24 patients
- Predominantly erythema only, 3 patients had pain, bruising and induration – all grade 1

Systemic adverse events

- All events were CTC grade 1 or 2. The majority were not definitely attributed to vaccination
- 12 patients experienced flu-like symptoms and night sweats
- Vitiligo was experienced by 3 patients
- All except 3 patients experienced anaemia. Five patients required a blood transfusion; all other anaemia was managed by iron supplements. Anaemia resulted from disease burden but may have been exacerbated by repeated venesection for dendritic cell preparation

Clinical Outcome

- 17 patients receiving > 1 cycle experienced progressive disease on-trial
- 2 patients – stable disease on-trial
- 1 patient – >50% reduction in lung metastases on CT scan and complete regression of cutaneous lesions. One new skin lesion was resected. This patient received 14 cycles of treatment
- 2 patients – partial response by RECIST
- Post cycle 4 – reduction in volume of lesions in liver, increase in size of lesions in lungs
- 6 weeks post cycle 4 – there was a dramatic improvement in the lung disease on chest X ray, confirmed on CT 12 weeks post cycle 4
- Post additional 4 cycles – further reduction in volume in liver and lungs but progressive disease based on new skeletal metastasis

Conclusion

There is clear evidence of biological activity for this vaccine. Current development strategy includes:

- vaccine development to identify the best of several non-viral transfection methods into dendritic cells
- combination treatment – initially exploring the pattern and kinetics of lymphocyte suppression following cyclophosphamide bolus treatment: selective depletion of suppressor immune cells might facilitate responses to the vaccine if cyclophosphamide and vaccination are used in sequence

GTAC 055: Gene Directed Enzyme Prodrug Therapy for the Treatment of Prostate Cancer (Phase I Intratumoural)

The Gene Directed Enzyme Prodrug Therapy was made up of two components: an adenovirus (CTL102) encoding a gene (*ntr*) expressing nitroreductase (NTR) under the control of a cytomegalovirus promoter, and an inactive prodrug (CB1954) which is converted to a potent cytotoxic metabolite by NTR. The primary objective of this study was to investigate the safety and tolerability of direct injection of escalating doses of CTL102 into primary prostate cancers and locally recurrent prostate cancers.

A total of 39 patients entered the study. These included 20 patients who had localized prostate cancer for which there was a clinical need for radical prostatectomy and who received CTL102 only (operable patients). 19 patients had locally recurrent prostate cancer (therapeutic patients); they received both CTL102 and CB1954. 14 patients received two cycles of treatment.

CTL102 was administered intraprostatically and doses were escalated in cohorts of at least three patients per dose level (1×10^{10} to 1×10^{12} particles per tumour). Cohorts of therapeutic patients received escalating doses of CTL102 followed two days later by intravenous CB1954 at a fixed dose of 24 mg/m^2.

The majority of adverse events were reported during the 3 months following CTL102 administration, only 19% of which were considered to be probably or highly probably related to the study drug(s). Most adverse events were mild and transient and there was no apparent relationship between CTL102 dose and incidence. Gastrointestinal disorders and abnormal liver function tests were most commonly reported over all CTL102 dose cohorts, consistent with the expected effects of CTL102 and/or CB1954. There were few reports of dose limiting toxicity and no potential immune toxicity to CTL102 was indicated. In those patients who received two treatment cycles, there were no apparent increases in adverse events after the second cycle.

The main indicator of efficacy was the level of *ntr*-expression in excised tumour samples in the operable patients. This acted as a guide to the success of the delivery of the virus to prostate tumour cells and surrounding tissues. There was a dose-dependent increase in *ntr*-expression through the cohorts, with no *ntr*-expression at the lowest cohort, showing the specificity of the approach. The study was not formally designed to evaluate 'therapeutic' efficacy but the opportunity to investigate the therapeutic response was taken: prostate specific antigen (PSA) levels were measured on a regular basis throughout the study and follow-up to track clinical response. Preliminary results suggest that although no evidence of effective lowering of PSA levels was observed, PSA levels remained generally stable throughout the study. In early evaluations of the tumours (at Week 4), partial response or stable disease was concluded.

In summary, this study indicates that the combination of CTL102/CB1954 is a feasible, repeatable and well-tolerated approach to targeted treatment for patients with primary and recurrent prostate cancers.

4.3 CARDIOVASCULAR DISEASE GENE THERAPY TRIALS

GTAC 051: Efficacy and Safety of Ad5FGF-4 in Patients with Stable Angina

In patients with severe recurrent angina, collateral formation is inadequate. Therefore, stimulating collateral vessel formation in the hearts of angina patients is a novel therapeutic approach. Preclinical studies with intracoronary administration of Ad5FGF-4 (replication deficient, EIA/E1B deleted, human adenovirus serotype 5 with human FGF-4 gene insert) in a pig model of chronic, stress-induced myocardial ischemia showed that the product is effective and safe (Gao et al, Human Gene Ther., 2004). In the first ascending-dose clinical trial in patients with refractory angina (AGENT [Angiogenic GENe Therapy]-1; Grines et al, Circulation, 2002) high first-pass product clearance by the heart and preliminary evidence of efficacy were demonstrated. In a subsequent myocardial stress perfusion study (AGENT-2), single intracoronary administration of Ad5FGF-4 increased blood flow in the ischemic region of the patient's heart (Grines et al, JACC, 2003). Based on these results, the phase 2b/3 AGENT-3 trial was initiated by Berlex in the US, and AGENT-4 was initiated by Schering AG in Europe, Latin America, and Canada. These trials enrolled a total of 532 patients under nearly identical protocols. The AGENT-3 trial was initiated in October 2001 and the AGENT-4 trial in March 2002.

Enrolment was stopped for both trials in January 2004, when a planned interim analysis of the AGENT-3 trial revealed the study was unlikely to yield a statistically significant result on the primary efficacy end point of change from baseline in exercise treadmill time duration at 12 weeks.

In October 2005, Cardium Therapeutics Inc licensed the product from Schering AG and performed a pooled data analysis from the nearly identical AGENT-3 and AGENT-4 trials to investigate possible treatment effects on primary and secondary end points in prespecified subgroups. The effect of placebo was large and no different to active treatment in men, but the placebo effect in women was negligible and the treatment effect was significantly greater than placebo. A statistically significant, gender-specific beneficial effect of Ad5FGF-4 was found on total ETT time, time to 1 mm ST-segment depression, time to angina, and Canadian Cardiovascular Society class in women (Henry et al, JACC 2007). The potential importance of the observed gender-specific angiogenic response on the clinical treatment of refractory angina is being evaluated in the recently launched phase 3 AWARE clinical trial.

SECTION 5: ANNEXES

ANNEX A: GLOSSARY

Please see the GTAC website: www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm

ANNEX B: TERMS OF REFERENCE

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

- To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;
- To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities – the Medicines and Healthcare products Regulatory Agency (MHRA), the Health and Safety Executive (HSE), and the Department for Environment Food and Rural Affairs (DEFRA);
- To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee has a responsibility for:

(a) Providing advice for applicants on:

1. The content of proposals, including the details of protocols, for gene therapy research on human subjects;
2. The design and conduct of the research;
3. The facilities necessary for the proper conduct of the research;
4. The arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

(i) The clinical status of the subjects;

(ii) The scientific quality of the proposal;

(iii) The scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;

(iv) Whether the clinical course of the particular disorder is known sufficiently well for the outcomes of therapy to be assessable;

(v) Sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject);

(vi) The potential benefits and risks for the subject of what is proposed.

In 2008 GTAC's terms of reference were updated. Please see the website for the latest information www.advisorybodies.doh.gov.uk/genetics/gtac/index.htm

ANNEX C: MEMBERSHIP OF GTAC

GTAC MEMBERS

- Professor Martin Gore (Chairman), Consultant Medical Oncologist, The Royal Marsden Hospital, London.
- Dr Richard Ashcroft, Medical Ethicist, Barts and the London NHS Trust.
- Professor Andrew Baker, Professor of Molecular Medicine, University of Glasgow.
- Dr Kathleen Bamford, Consultant Medical Microbiologist and Visiting Professor, Imperial College Healthcare NHS Trust and Imperial College London.
- Mrs Deborah Beirne, Senior Research Nurse, St. James's Hospital, Leeds.
- Professor Hilary Calvert, Professor of Medical Oncology and Clinical Director of the Northern Institute for Cancer Research, University of Newcastle Upon Tyne.
- Professor Mary Collins, Division of Infection and Immunity, Royal Free and University College Medical School, University College London.
- Ms Claire Foster, Policy Adviser, Medical Ethics, Archbishops' Council.
- Professor Terence Hamblin, Professor of Immunohaematology, University of Southampton; Consultant Haematologist with Southampton University Hospitals and Kings College Hospital, London.
- Dr Peter Harris, CMO, Oxigene Inc (until July 2007); CMO, Algeta (from October 2007).
- Professor David Harrison (Vice-Chairman), Professor of Pathology and Medical Researcher, Department of Pathology, Edinburgh University.
- Mr Michael Harrison (alternate Vice-Chairman), Barrister, London.
- Professor Nicholas Lemoine, Professor of Molecular Pathology, Institute of Cancer, Queen Mary University of London.
- Dr Adrian Lepper, Chartered Engineer, Hertfordshire.
- Dr Stephen Minger, Director, Stem Cell Biology Laboratory, Wolfson Centre for Age-Related Disease, KCL, London.
- Right Reverend Dr Lee Rayfield, Bishop of Swindon and former immunologist.
- Mrs Fiona Sandford, Patient Advocate, Hertfordshire.
- Dr Michael Waterhouse, Television Producer and Author, Southborough.

Observers

Medicines and Healthcare products Regulatory Agency (MHRA):

- Dr Sharon Longhurst, Dr Riaz Zuhrie

Health and Safety Executive:

- Dr Paul Logan, Dr David Brown

Secretariat (Department of Health)

- Dr Monika Preuss
- Ing. Daniel Gooch
- Miss Joanna Edwards
- Mrs Halina Pounds
- Mrs Margaret Straughan

Payment of members

Fees are payable to members at a rate of £148.59 per meeting, £180.40 per meeting for the Chair. Members are reimbursed for all reasonable travelling expenses.

Co-opted Members

Dr Colin Steward, Consultant Senior Lecturer in Bone Marrow Transplantation of Metabolic & Genetic Diseases at Bristol Royal Hospital for Sick Children (May meeting to advise on the X-SCID application).

Dr Vivian Mautner, Cancer Research UK, Institute for Cancer studies, University of Birmingham (December meeting to advise on infectious disease protocol).

Members' attendance in 2007

Name	Dates of meetings attended
Professor Martin Gore	May, July, October, December
Professor David Harrison	February, May, July, October, December
Mr Michael Harrison	February, May, July, October
Professor Richard Ashcroft	February, May, July, October
Professor Andrew Baker	February, May, July, October, December
Dr Kathleen Bamford	February, May, July, October, December
Ms Deborah Beirne	February, May, July, October, December
Professor Hilary Calvert	May, July, October, December
Professor Mary Collins	February, May, July, October, December (from item 8)
Ms Claire Foster	May, October, December (until item 8)
Professor Terry Hamblin	February, May, July, October, December
Dr Peter Harris	February, May, July, October
Professor Nick Lemoine	February, July, December
Dr Adrian Lepper	February, May, July, October, December
Dr Stephen Minger	February, May, July, October
Bishop Dr Lee Rayfield	February, May, July, October
Mrs Fiona Sandford	May, October, December
Dr Michael Waterhouse	May, October, December

ANNEX D: REGISTER OF MEMBERS' INTERESTS

GTAC Member	Declared interests
Dr Richard Ashcroft	None
Professor Andrew Baker	None
Dr Kathleen Bamford	Chair of HHT Gene Therapy and Genetic modification Safety Committee Companies who have paid expenses or provided financial support for attendance at meetings, or paid honoraria include Pfizer/Pharmacia Ltd, Gilead Ltd, Wyeth Ltd, Bayer Ltd, Baxter Research funded by Pfizer Advisory board Pfizer
Mrs Deborah Beirne	Work involves gene therapy trials
Professor Hilary Calvert	Occasional Advisory boards for: Novartis, GSK, Schering AG, Nerviano Pharmaceuticals, Kudos Pharmaceuticals/ AstraZeneca, Eli Lilly, Schering Plough Research grants to Prof Calvert/the Department from: Eli Lilly, Pfizer, OSI
Professor Mary Collins	None
Ms Claire M Foster	None
Professor Martin Gore	Companies who have paid honorariums, expenses and financial support for clinical trials and research include: Cobra Therapeutics Ltd, Genta Inc, ML Laboratoties PLC, Onyx Advisory Board of Onyx Advisor to Cambridge Antibody Technology
Professor Terence Hamblin	Ad hoc consultant to Roche Pharmaceuticals, Genzyme, Protherics and AstraZeneca Paid employment as Editor of Leukemia Research by Elsevier Publications
Dr Peter Harris	Oxigene Inc (share option holder) Ad hoc consultant to Crusade Laboratories Ad hoc consultant to Spirogen Ltd

Professor David Harrison	Consultancies: University of Florida; The Forensic Institute; Crusade Laboratories (dormant); Director, Edinburgh Cancer Research UK Clinical Centre
	Shareholdings: The Forensic Institute
	Chair, EMMS Nazareth (overseas healthcare charity), unpaid; Director, Emmanuel Healthcare (overseas healthcare charity), unpaid
	Indirect support: Research funds from CRUK, MRC, Wellcome Trust, Chief Scientist Office, Scotland
Mr Michael Harrison	Managing director of Bioethics Consulting Ltd (dormant)
	Independent practising barrister working in the field. Interests are declared as appropriate
Professor Nicholas Lemoine	Consultant for Medical Solutions Ltd
	Joint project funding for gene therapy agent with Cronos Therapeutics Limited from CR-UK Development Fund
	Co-investigator on trial protocol with an agent from BioVex Ltd
Dr Adrian Lepper	Secretary to the Board, eLearning Holding company
	Member of Corporation and Governor, West Herts College
	Independent consultancy assignments
	Chair of Trustees – Care Co-ordination Network (UK)
	Wife has a small shareholding in GlaxoSmithKline
Dr Stephen Minger	PhD studentships jointly funded by GSK/MRC and Novartis/MRC; received honoraria for research seminars from GSK, Novartis, Merck
	Co-Organiser of London Regenerative Medicine Network, which is partially funded by GSK
	Member of Progress Educational Trust Advisory Panel
	Paid consultant to Vertex Pharmaceutical Company (fees placed into research accounts)
	Unpaid advisor to Nikon Corp

Bishop Dr Lee Rayfield	None
Mrs Fiona Sandford	None
Dr Michael Waterhouse	None

ANNEX E: EXTERNAL EXPERT ADVISERS TO GTAC

GTAC is extremely grateful to all its expert advisers for their support in the review of applications and for their input of expertise and advice in 2007. These included:

Dr Bridget Bax, Dept of Child Health, St George's Hospital Medical School, London

Professor Keith Channon, University of Oxford, Department of Cardiovascular Medicine, John Radcliffe Hospital

Dr Jeff Chamberlain, Department of Neurology, University of Washington School of Medicine, Seattle, USA

Professor John Dodge, Big Wood Barn, Monmouthshire

Professor Hazel Dockrell, Head, Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine

Dr Sarah George, Bristol Heart Institute, Bristol Royal Infirmary

Professor Brian Greenwood, London School of Hygiene & Tropical Medicine

Professor Nagy Habib, Head of Liver and Pancreas Surgery, Imperial College London, Hammersmith Hospital

Professor Alan Knox, Centre for Respiratory Research, Medical and Surgical Sciences, City Hospital, Nottingham

Dr Walter Koch, Director of the Centre for Translational Medicine, Pennsylvania, USA

Dr Keith Leppard, Department of Biological Sciences, University of Warwick

Dr Mark Middleton, Churchill Hospital, Oxford

Professor John McMurray, Division of Cardiovascular Medicine, Department of Cardiology, Western Infirmary, Glasgow

Professor Jim Neil, Molecular Oncology Laboratory, Institute of Comparative Medicine, University of Glasgow Veterinary School

Professor Norman Nevin, Emeritus Professor of Medical Genetics, Queen's University, Belfast

Dr Barry Peters, Reader & Honorary Consultant Physician, Head of Academic Unit of HIV & STDs, St Thomas' Hospital, London

Professor Pat Price, Division of Cancer Studies, Faculty of Medical and Human Sciences, University of Manchester

Dr Sunil Shunak, Department of Infectious Diseases, Imperial College at Hammersmith Hospital, London

Professor Peter Stern, Department of Molecular Biology, Christie Hospital NHS Trust, Manchester

Dr Robin Thorpe, National Institute for Biological Standards and Control

Professor Keith Wheatley, University of Birmingham Clinical Trials Unit, Birmingham

ANNEX F: REPORT OF THE REVIEW OF THE FLAGGING PROJECT

NOTE OF THE DISCUSSION HELD BY GTAC ON 21 FEBRUARY 2007

Present:

GTAC Members

- Professor David Harrison (Chair)
- Dr Lee Rayfield
- Dr Kathy Bamford
- Professor Andy Baker
- Mrs Debbie Beirne
- Dr Adrian Lepper
- Professor Richard Ashcroft
- Professor Terry Hamblin
- Dr Stephen Minger
- Professor Mary Collins

DH Secretariat

- Dr Monika Preuss
- Mr Daniel Gooch
- Miss Joanna Edwards

Observers

- Dr Riaz Zuhrie (MHRA)
- Dr Sharon Longhurst (MHRA)

Invitees

- Professor Liz Miller (HPA)
- Mr Mark Noterman (DH)
- Dr Jonathan Fistein (National Programme for IT)
- Ms Kathryn Anderson (ONS)
- Mrs Diane Pryce (ONS)
- Dr Elaine Godfrey (MHRA)
- Dr Julie Williams (MHRA)
- Professor Deborah Ashby (Queen Mary, University of London)

1 The Chair opened the meeting by welcoming everyone to the discussion on the review of the GTAC/DH flagging project. All participants had received a briefing document which outlined the project and progress so far plus background reading material.

2 The Chair summarised the purpose to the meeting. The Secretariat had prepared an analysis of the flagging returns to date. This was a good opportunity to review the project and its objectives. The main points were:

- In 1999/2000, GTAC/DH initiated the pilot of a research study called "long-term monitoring of patients participating in gene therapy" (the flagging project), a mechanism for traceability and passive follow-up of gene therapy patients.
- Under the pilot, no active monitoring of patients' health takes place, the only information available about flagged patients is whether they are alive and if not, the cause of death.
- A second phase of the project foresaw the possibility of writing to patients' GPs to ask for health information. This was not actioned because the number of flagged patients alive was very small, making data analysis of little use. Consequently, the project was operating as a means by which to flag patients rather than a means to find out about their health.

3 There was consensus that the pilot project has been visionary and progressive as the first proposal of this kind when it was initiated in 1999/2000. However, now was the time to take stock in light of the results and regulatory developments affecting clinical research since 1999/2000 (in particular the Clinical Trials Regulations 2004).

4 The Chair invited Prof Ashcroft to report to GTAC the outcome of a meeting which had been held the previous month of a small flagging project working party (GTAC members Mrs Sandford, Mr Harrison, Prof Ashcroft), and the Secretariat. The note of the meeting was appended in the papers. The following main points were made:

- There were a number of concerns with the project's methodology that needed resolving (on reporting and consent).
- Flagging returns were much below the expected rate; there was limited uptake by investigators and/or patients. This suggested low confidence in the project by trialists and/or patients.
- The analysis of flagging data was confounded by multiple variables such as vector type, patient population, disease, time and low patient numbers.
- Over 80% of participants who received higher risk products took part in cancer clinical trials where patients are critically ill; two thirds of these patients were now dead because of disease progression.
- In conclusion, the working group had considered that the project as currently run was of limited value. There may be a case for flagging of some gene therapy patients but a new methodology would need to be developed. The data as currently collected was not useful in terms of safety monitoring.

5 The Chair opened the debate up to the wider group. The following contributions were made:

I Issues to do with data analysis:

- The majority of flags concern patients who are terminally ill, however this may change as the technology progresses to being applied in patients with non life threatening diseases.
- For valuable, interpretable data to be generated, an appropriate control group is required, for instance the same patient population receiving alternative treatment (as in placebo-controlled trials).
- Low recruitment and clinician buy-in makes data analysis difficult.
- Useful data may be generated from low numbers but this requires clearly defined risks and a specification as to precisely what long-term effect is anticipated, probably on a trial-by-trial basis rather than across a wide variety of vectors and patients. An example may be the DH-led surveillance of people thought to be at risk of contracting vCJD from blood transfusions. Here, the anticipated outcome is well defined (neurological disorder); however, for gene therapy this is considerably more complex.
- Many clinical trials of gene therapy recruit internationally and it would be helpful to be able to draw from as wide a patient pool as possible. As a first step this may be achieved across Europe, where greater harmonisation of clinical trials is an objective.
- The national programme for IT (NHS Connecting for Health) may provide a good platform for data collection and analysis but this is some years away.

II Issues to do with utility:

- It was noted that many gene therapy patients are currently followed for life, in particular when enrolled in cancer protocols (over 70% of gene therapy trials) where patients are critically ill, usually have had previous exposure to harmful agents (chemotherapy, radiotherapy etc), and where time of survival often is a trial endpoint. In the paediatric population (for instance in patients with SCID) by the nature of their disease, patients already are under regular clinical surveillance.
- The Clinical Trials Regulations 2004 formalised adverse event reporting to the competent authority (MHRA) and research ethics committees in a way that was not the case in 1999/2000. This concerns adverse events that occur during a clinical trial; there is no formal mechanism for reporting delayed events that occur when patient follow-up as per protocol has finished. However, in cases where there is a recognised increased risk of delayed effects, clinical trial protocols acknowledge and address this.

- In conclusion, it was considered that the flagging project, with its emphasis on patient traceability (rather than active follow-up), was not yielding useful safety data and did not add value to safety monitoring requirements under the Clinical Trials Regulations. The methodology would have to be amended significantly to address these concerns; as it was operating, it had become redundant. However, the concept of long-term monitoring of (some) gene therapy recipients remains valid.

6 Conclusion: There was consensus agreement that the project should be closed to further recruitment. While there may be a case for long-term follow-up under some circumstances, GTAC, an ethics committee, would not be the appropriate body to do safety monitoring. GTAC may however wish to continue to engage in this topic.

7 The group continued to discuss options for how, and by which body, safety monitoring could be taken up. The group noted two relevant initiatives:

- Guidance by the FDA on observing subjects for delayed adverse events following gene therapy (issued in November 06);
- An upcoming concept paper by EMEA's Gene Therapy Working Party on long-term monitoring (thought to go to consultation in the next 6 months). GTAC expressed the hope that it will be given the opportunity to comment on this document at an early stage.

8 The group went on to discuss briefly the circumstances under which there may be a case to provide for long-term follow-up:

- Long-term monitoring is not relevant to all patients but it depends on the vector, transgene and patient population; the greatest concern arises from integrating vectors.
- While there is value in looking at each vector individually (as per FDA proposal), there is also merit in grouping together certain vectors (for instance retroviral and lentiviral vectors).
- Careful consideration has been given to the cost of long-term monitoring, the value it adds, the level of active monitoring, and imposition on patients. A long-term monitoring protocol needs to have very clear objectives, be hypothesis driven, and be based on appropriate risk assessment (for instance adopting from risk management plans as they need to be in place at the point of licensing).
- Safety monitoring of patients enrolled in clinical trials is the responsibility of the MHRA, rather than that of an ethics committee. GTAC was invited to write to MHRA with its recommendations as to when long-term monitoring should be built into a trial protocol.
- The need for patient follow-up after treatment with an advanced therapy medicinal product (such as gene therapy) has been recognised in European medicines legislation (Commission Directive 2003/63/EC), and will be further specified by the draft Regulation on Advanced Therapy Medicinal Products (currently in negotiation).

9 The Chair then moved on the discussion to the immediate next steps and the practicalities of closing the project. The following was agreed:

- Chief investigators of trials currently subject to the flagging project need to be informed of project closure and outstanding returns should be requested to complete the data set. This may form the basis of a publication (for instance GTAC annual report and/or other).
- Thought must be given to informing patients who are currently enrolled in the flagging study.
- Thought remains to be given to whether existing flags should be removed from the NHS Central Register (NHSCR).
- Careful consideration has be given to the cost of long-term monitoring, the value it adds, level of active monitoring, and imposition on patients. A long-term monitoring protocol needs to have very clear objectives, be hypothesis driven, and be based on appropriate risk assessment (for instance adopting from risk management plans as they need to be in place at the point of licensing).
- Safety monitoring of patients enrolled in clinical trials is the responsibility of the MHRA, rather than that of an ethics committee. GTAC was invited to write to MHRA with its recommendations as to when long-term monitoring should be built into a trial protocol.
- The need for patient follow-up after treatment with an advanced therapy medicinal product (such as gene therapy) has been recognised in European medicines legislation (Commission Directive 2003/63/EC), and will be further specified by the draft Regulation on Advanced Therapy Medicinal Products (currently in negotiation).

10 The Chair summarised the actions arising from the meeting, thanked everyone for their time and expertise, and closed the meeting.

GTAC Secretariat
March 2007

ANNEX G: SUMMARY OF UK GENE THERAPY CLINICAL RESEARCH 1993-2007

AN ANALYSIS OF UK CLINICAL GENE THERAPY: 1993 – 2007

Since 1993, when the first gene therapy study was conducted in the UK, GTAC has processed 155 applications to conduct clinical trials. Of these, 126 applications were approved (or conditionally approved) and 29 applications were either declined by GTAC or never commenced because they were subsequently withdrawn. The relevant 126 gene therapy trials are analysed below.

In these 126 trials, over 1,663 patients were enrolled by December 2007 – 1,262, 960 and 894 patients by December 2006, 2005 and 2004 respectively (data incomplete as open trials often do not report current recruitment rates). As of December 2007, 72 trials (57%) are closed and 54 trials (43%) are open or due to open. 1,159 of the 1,663 patients were enrolled across the 72 closed studies, and 504 patients were enrolled in the 54 open trials.

The following figures analyse the studies in terms of the year in which they were approved (Figure 1), the vector system used to deliver the therapeutic genes (Figure 2), and the disease (Figure 3). As shown in Figure 3, 62% of all approved UK gene therapy trials (78 in total) are for the treatment of cancers. Interestingly, this figure is down from previous years, where cancer trials dominated with over 70% of applications. Figure 4 breaks down this data in more detail.

Table 1 shows where UK gene therapy stands in relation to trials in Europe and worldwide. (source: The Journal of Gene Medicine, March 2008)

Figure 1: GTAC approved trials by year

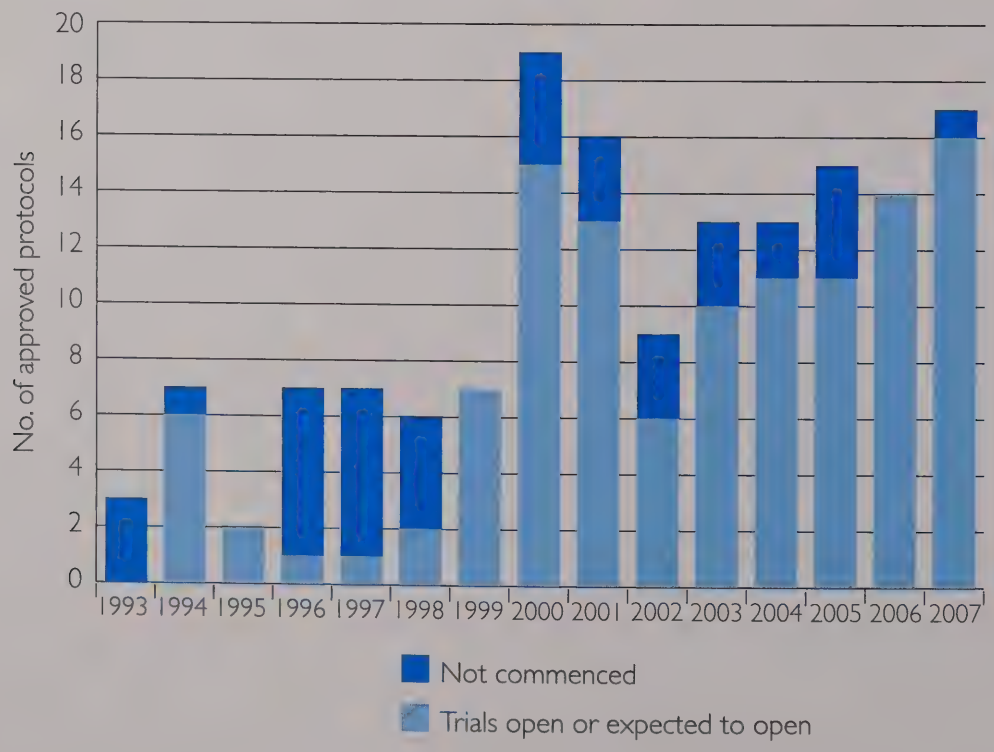
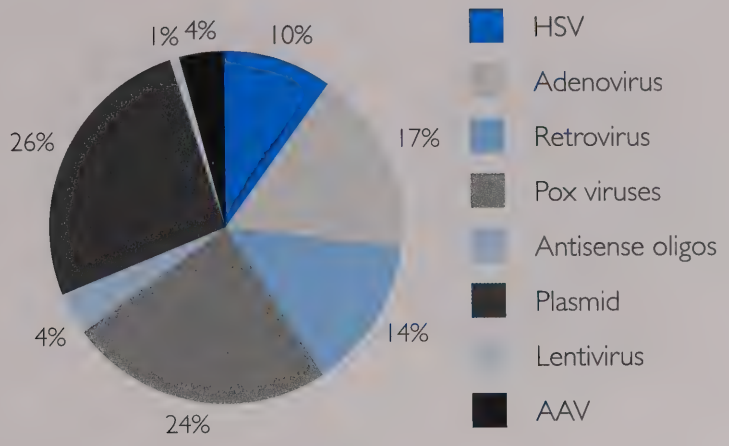
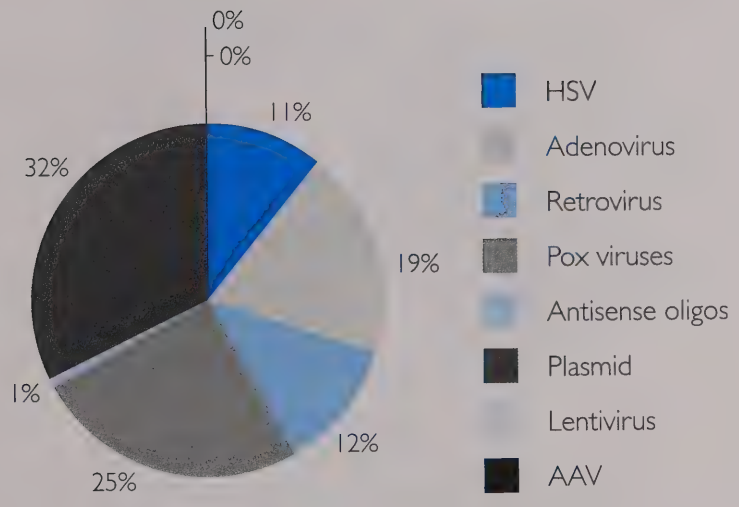


Figure 2: GTAC approved trials by vector system

a. All trials (n=126)



b. Closed trials (n=73)



c. Open trials (n=53)

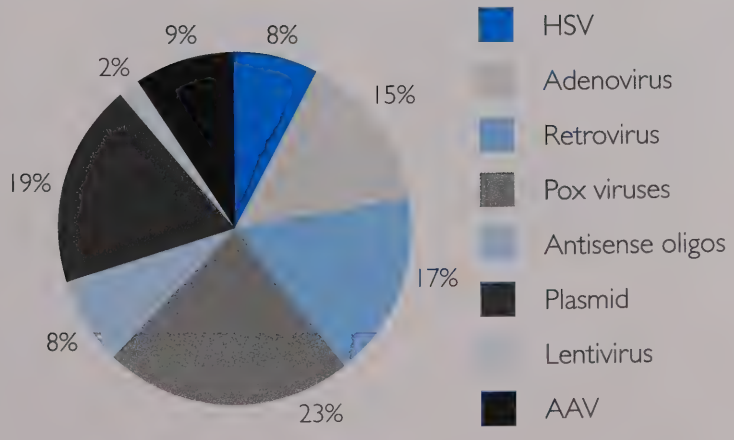
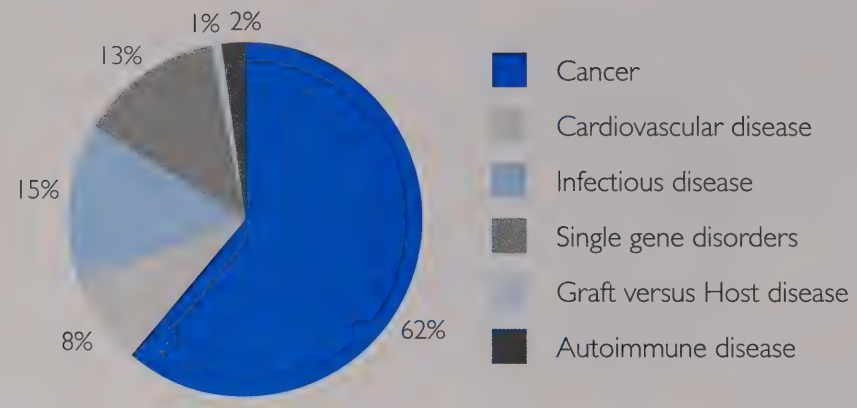
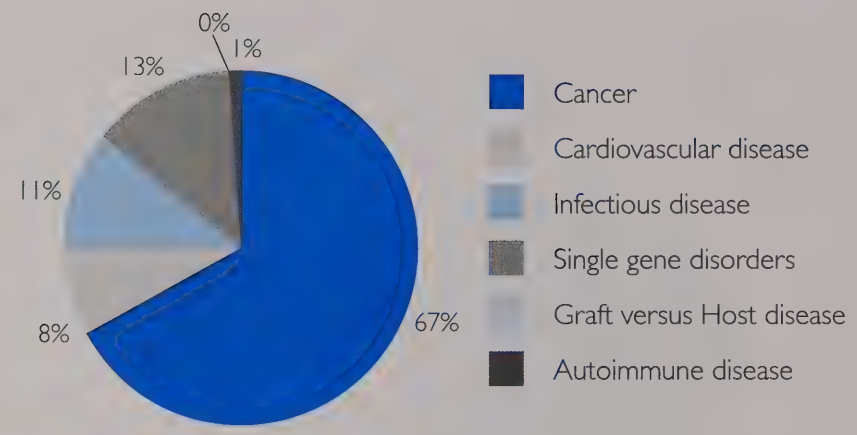


Figure 3: GTAC approved trials by disease

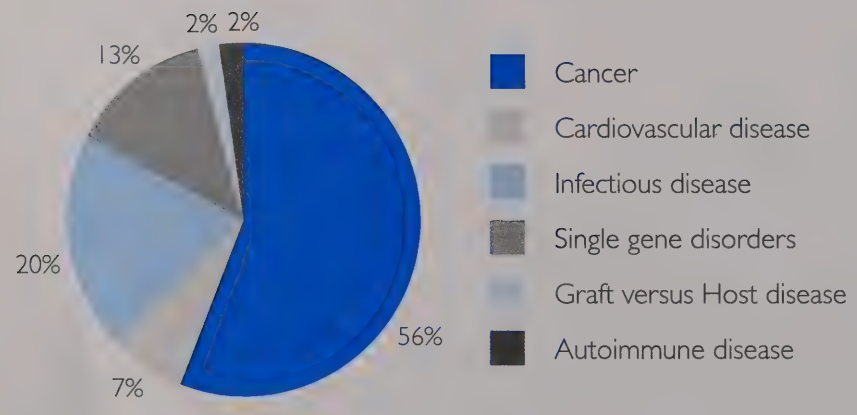
a. All trials (n=126)



b. Closed trials (n=72)



c. Open trials (n=54)



d. Patients enrolled in closed trials (n=1,111). (see **b**).

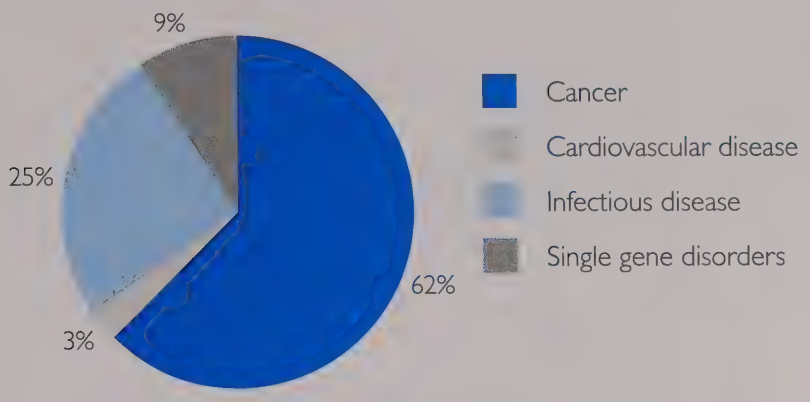
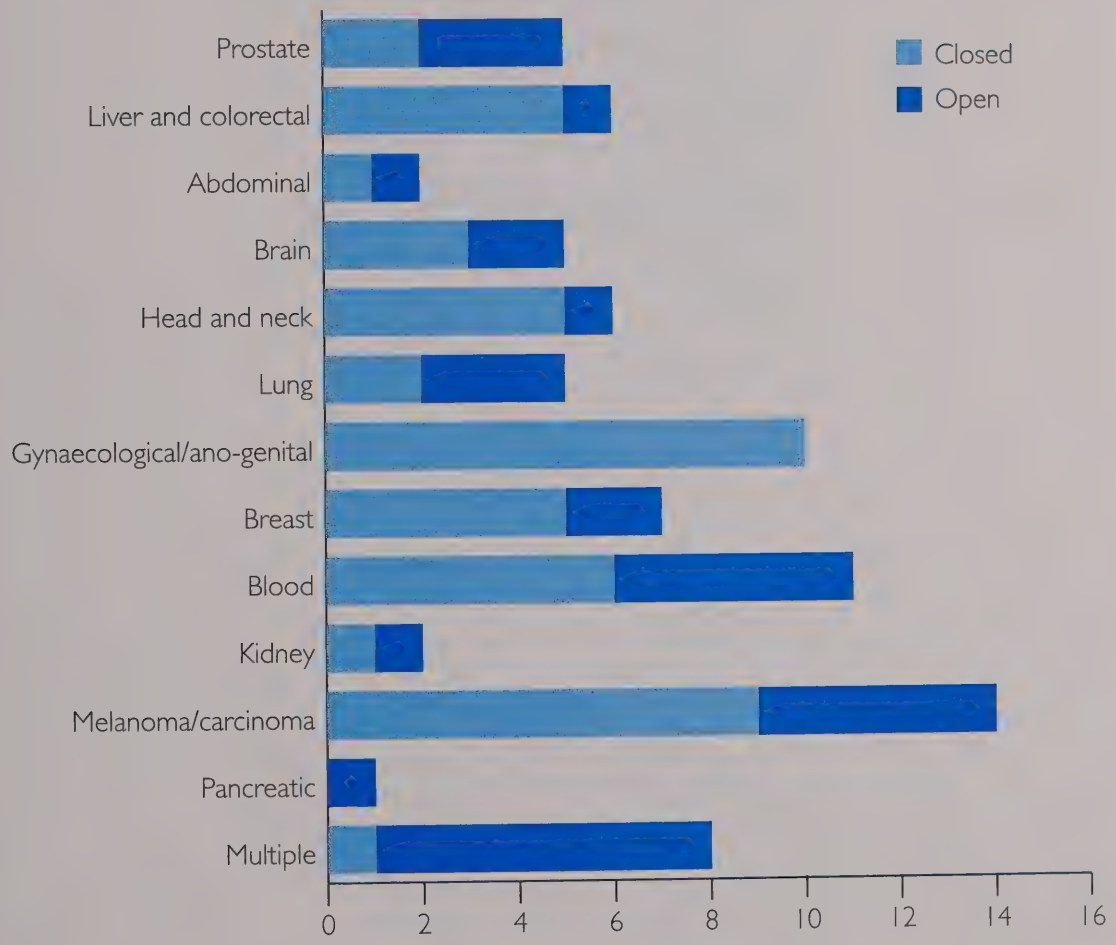


Figure 4: GTAC approved cancer trials (n = 78)

a. Number of cancer trials (30 open and 48 closed)



b. Patients enrolled in closed cancer trials (n=715)

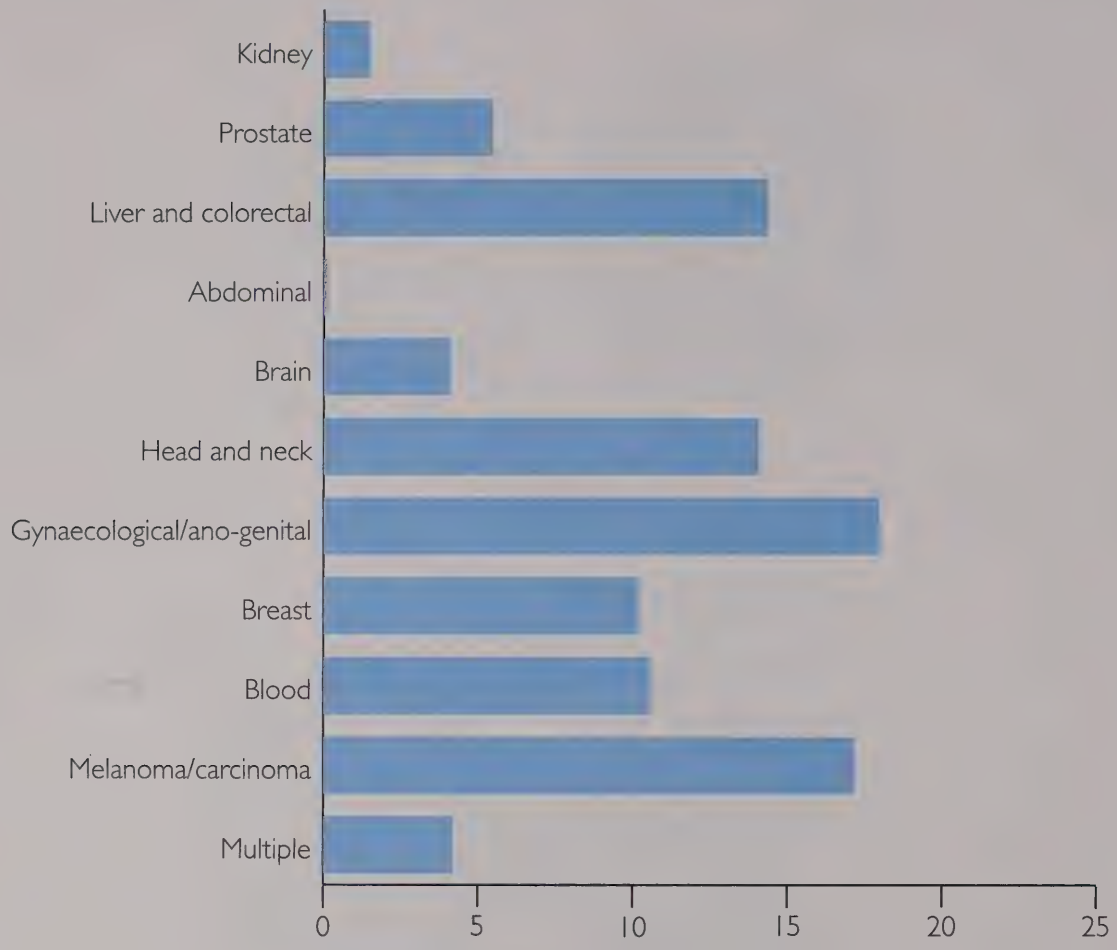


Table 1: Gene Therapy trials worldwide and in Europe (source: Journal of Gene Medicine, www.wiley.co.uk/genetherapy/clinical/, March 2008).

Country	Europe	Worldwide
Australia		2.0 %
Austria	0.6%	0.1 %
Belgium	5.3%	1.4 %
Canada		1.3 %
China		0.6 %
Czech Republic	0.3%	0.1 %
Denmark	0.6%	0.1 %
Egypt		0.1 %
Finland	0.8%	0.2 %
France	5.6%	1.5 %
Germany	20.6%	5.5 %
Israel		0.4 %
Italy	4.2%	1.1 %
Japan		1.2 %
Mexico		0.1 %
Netherlands	4.4%	1.2 %
New Zealand		0.1 %
Norway	1.1%	0.3 %
Poland	1.7%	0.4 %
Russia		0.1 %
Singapore		0.1 %
South Korea		0.3 %
Spain	1.1%	0.3 %
Sweden	0.6%	0.1 %
Switzerland	11.7%	3.1 %
Taiwan		0.1 %
UK	**41.7%**	**11.1 %**
USA		66 %
Multi-country		0.9 %
	100%	100%

LATEST UK GENE THERAPY RESEARCH 1993-2007 (JANUARY 2008)

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
01	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	SCID-ADA	Institute of Child Health/ Great Ormond Street Hospital	1–93	Retrovirus	ADA	pOAM-P1	1 CLOSED
02	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Royal Brompton Hospital	3–93	Plasmid	CFTR	*E. coli* DM5a	15 CLOSED
03	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	MRC Cambridge	7–93	Plasmid	anti-idiotype immunoglobulin	*E. coli*	7 CLOSED
04	Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow	Neuroblastoma	ICRF Bristol	2–94	Retrovirus	LNL-6/neo G1N-neo	PA317	Trial withdrawn
05	Gene therapy for metastatic melanoma: assessment of expression of DNA constructs directly injected into metastases	Metastatic melanoma	ICRF Oxford	5–94	Plasmid	IL-2	*E. coli* JM109	23 CLOSED
06	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secrete IL-2	Metastatic melanoma	Institute of Cancer Research, Royal Marsden Hospital	2–94	Retrovirus	IL-2	GP+env AM12	12 CLOSED
07	Towards gene therapy for cystic fibrosis	CF Nasal trial	Oxford, Cambridge	2–94	Plasmid	CFTR	*E. coli*	18 CLOSED
08	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Edinburgh	5–94	Plasmid	CFTR	*E. coli*	16 CLOSED
09	Gene Therapy Research for Cystic Fibrosis	CF Lung trial	Royal Brompton Hospital	9–94	Plasmid	CFTR	*E. coli*	16 of 16 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
10	Transfer of the human multi-drug resistance gene into the haemopoietic cells of patients undergoing high-dose therapy and autologous stem cell transplantation for malignant lymphoma	Lymphoma	University College London Medical School	12–94	Retrovirus	MDR-1	AMI2M1	3 CLOSED
11	Genetic prodrug activation therapy for breast cancer	Breast cancer	Hammersmith Hospital	10–95	Plasmid	Cytosine deaminase	*E. coli*	12 CLOSED
12	Use of a recombinant vaccinia virus for therapy of cervical cancer	Cervical carcinoma	University of Wales, Cardiff	6–95	Vaccinia	TA-HPV	MRC5	1+8 CLOSED
12A	Use of a recombinant vaccinia vaccine (TA-HPV) to treat cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5–96	Vaccinia	HPV E6 and E7	MRC5	12 CLOSED
12B	Use of a recombinant vaccinia vaccine (TA-HPV) to treat cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff; University of Manchester	8–97	Vaccinia	HPV E6 and E7	MRC5	8 CLOSED
12C	Use of recombinant vaccinia vaccine (TA-HPV) to treat vulval intraepithelial neoplasia III	Vulval intraepithelial neoplasia III	St Mary's Hospital, Manchester	1–00	Vaccinia	HPV E6 and E7	MRC5	18 CLOSED
12 D	Use of a recombinant vaccinia vaccine (TA-HPV) to treat ano-genital intraepithelial neoplasia III	Ano-genital intraepithelial neoplasia III	Addenbrooke's Hospital, Cambridge	4–00	Vaccinia	HPV E6 and E7	MRC5	12 CLOSED
13	A proposal to study the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation (Hurlers syndrome)	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	12–95	Retrovirus	pLX	GP+env AM12	3 CLOSED
14	Phase I, open-label, dose-escalation trial of intra-tumoral injection with an E1B attenuated adenovirus ONYX-015, into recurrent and locally advanced p53(-) squamous cell tumours of the head and neck	Head and neck cancer	Beatson Oncology Centre, Glasgow	1–96	Adenovirus	E1B deleted	HEK293	22 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
14A	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent, chemotherapy naive squamous cell tumours of the head and neck	Head and neck cancer phase II study	Beatson Oncology Centre, Glasgow	7–97	Adenovirus	E1B deleted	HEK293	37 CLOSED
14 B	Phase I, open-label, dose-escalation trial of intraperitoneal injection with an E1B attenuated adenovirus in patients with recurrent/refractory ovarian carcinomas	Recurrent/ refractory ovarian cancer	Beatson Oncology Centre, Glasgow	2–97	Adenovirus	E1B deleted	HEK293	12 CLOSED
15	Towards gene therapy for Cystic Fibrosis	CF Nasal trial	Oxford/Cambridge/ Leeds/Manchester Consortium	5–96	Plasmid	CFTR	*E. coli*	11 CLOSED
16	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	Head and neck cancer	Institute of Cancer Research; Royal Marsden Hospital	9–96	Adenovirus	p53	HEK293	Trial never commenced in UK CLOSED
17	Gene therapy for Cystic Fibrosis delivery to nasal epithelium and lung by nebulisation of the pCFICFTR/#67	CF Lung and nasal trial	Royal Brompton Hospital	11–96	Plasmid	CFTR # 67	*E. coli* TGI	16 CLOSED
18	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	12–96	HSV	ICP34.5 deleted	BHK 21/C13	9 CLOSED
18A	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow; Institute of Neurological Sciences, Glasgow; Queen Elizabeth Hospital, Birmingham	7–99	HSV	ICP34.5 deleted	BHK 21/C13	12 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
18B	A study of the safety of the modified Herpes simplex virus (HSV 1716) when injected into tumour-bearing brain following resection of recurrent or newly diagnosed high grade glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	11–00	HSV	ICP34.5 deleted	BHK 21/C13	8 CLOSED
19	GT10115 radiation and infection of murine cells producing HSV TK vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed previously untreated glioblastoma (tumour site)	Glioblastoma	Beatson Oncology Centre, Glasgow; Institute of Neurological Sciences, Glasgow	3–97	Retrovirus	TK	PA317	Trial withdrawn
20	A clinical trial with Ad-5CMV-p53 vector in patients with ascites formation	Gastrointestinal cancer, malignant cancer ascites	Royal Marsden Hospital, London	4–97	Adenovirus	p53	Hek293	1 CLOSED
21	Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031)	Breast cancer	Guy's Hospital, London	11–97	Vaccinia	MUC-1 IL2	–	14 CLOSED
22	A multiple ascending-dose study evaluating the safety and the gene transduction into malignant cells after the administration of EIA-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER-2/neu	Ovarian cancer	The John Radcliffe Hospital, Oxford; Guy's and St Thomas's Cancer Centre, London; Royal Marsden Hospital, London; St George's Medical School, London.	9–97	Plasmid	E1A HER2/neu	*E. coli* STBL2	22 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
23	A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer (Phase I subcutaneous)	Colorectal cancer	Queen Elizabeth Hospital, Birmingham	3–98	Vaccinia	CEA	CV1	0 CLOSED
24	A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients	Ovarian cancer	City Hospital NHS Trust and University Hospital NHS Trust Birmingham	3–98	Adenovirus	Nitroreductase	HEK-293	0 CLOSED
25	A multiple ascending-dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoral injection with unresectable or metastatic head and neck tumours	Head and neck	Royal London Hospital; Charing Cross Hospital	Submission withdrawn	Plasmid	E1A	HEK293	Application withdrawn
26	A study of dose requirements, safety and local efficacy of intratumoral injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma	Malignant melanoma	Glasgow Western Infirmary and Southern General Hospital, Glasgow	9–98	HSV	ICP34.5 deleted	BHK-21/C13	5 CLOSED
27	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoral)	Breast cancer	The Churchill, Oxford	10–98	Retrovirus	Cytochrome P450	TEFLY-A	12 CLOSED
28	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours	Liver cancer	Hammersmith Hospital, London	Application withdrawn	Adenovirus	p53	HEK293	Application withdrawn

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
29A	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (LIFTT) EudraCT: 2005-002967-99	B-cell lymphoma	Royal Bournemouth Hospital; Southampton General Hospital; Christie Hospital Manchester	5–99	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	25 of 25 CLOSED
29B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogenic bone marrow transplantation for multiple myeloma "EDLI"	Multiple myeloma	Southampton General Hospital; Nottingham City Hospital; University College London	5–00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	3 of 15
29C	Phase I/II study of idiotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	Multiple myeloma	Royal Bournemouth Hospital; Southampton General Hospital; Nottingham City Hospital	4–00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	13 of 15 – 20
29D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFTT)	Chronic lymphocytic leukaemia	Royal Bournemouth Hospital; Southampton General Hospital	4–00	Plasmid	Idiotypic DNA vaccination	*E. coli JM109*	2 of 10 CLOSED
30	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal).	Ovarian cancer	Northern General Hospital, Sheffield	2–00	Retrovirus	Cytochrome P450	TEFLY-A	6 CLOSED
31	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (Phase I intratumoral)	Head and neck cancer	Queen Elizabeth Hospital, Birmingham; Royal Marsden Hospital, London	7–99	Adenovirus	Nitroreductase	PER-C6	7 of 30 CLOSED
32	Gene directed enzyme prodrug therapy for the treatment of liver cancer (Phase I intratumoral)	Liver cancer	Queen Elizabeth Hospital, Birmingham	7–99	Adenovirus	Nitroreductase	PER-C6	25 of 30 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
33	Phase I trial of immunotherapy with adenovirus-interferon-γ in malignant melanoma (intratumoral)	Malignant melanoma	St. George's Hospital, London	7–99	Adenovirus	IFN-γ	–	1 CLOSED
34	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian and primary intraperitoneal cancer (intraperitoneal)	Ovarian cancer	Royal Marsden Hospital, Christie Hospital/ CRC Institute for Cancer Studies, John Radcliffe Hospital	7–99	Adenovirus	p53	HEK293	1 CLOSED
35	Phase II trial of pre-operative intratumoral injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours	Head and neck cancer	Beatson Oncology Centre, Glasgow	7–99	Adenovirus	E1B deleted	HEK293	15 CLOSED
36	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD)	Peripheral arterial occlusive disease	St George's Hospital, London	10–00	Adenovirus	FGF-4	PER-C6	13 (2 UK) of 30 CLOSED
37	A Phase III study of quadruple HAART followed by double-blind randomisation to HIV vaccination with ALVAC-HIV and Remune or placebo	HIV	Chelsea & Westminster Hospital; Royal Free Hospital; Brighton General Hospital; University Hospital of Wales Cardiff	5–00	Canarypox	HIV-1 *env, gag*	AVIAN	8 of 15 CLOSED
38	A Phase I, open-label, dose-escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with metastatic melanoma	Malignant melanoma	Churchill Hospital, Oxford; Royal Marsden Hospital, London	5–00	HSV	hGMCSF	CR2C9 (Vero-derived)	10 CLOSED
39	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of TroVax in patients with metastatic colorectal cancer (Phase I i.m.)	Colorectal cancer	Christie Hospital NHS Trust, Manchester	10–00	Vaccinia	Human oncofoetal antigen 5T4	CEF	22 of 22 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
40	A Phase I dose escalation trial of an E1B attenuated adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	Bladder cancer	St James's University Hospital, Leeds	Conditional Approval 7–00	Adenovirus	E1B deleted	HEK293	Trial withdrawn
41	Randomised multi-centre trial evaluating two different vaccination schedules of MVA-MUC-1-IL-2 in women with metastatic breast cancer (Phase II i.m.)	Breast cancer	Guy's Hospital, London	Application withdrawn	Vaccinia	MUC-1, IL-2	CEF	Application withdrawn
42	Phase I study of melanoma poly-epitope DNA and melanoma poly-epitope modified vaccinia Ankara in patients with melanoma	Melanoma	The Churchill Hospital, Oxford	7–00	Vaccinia DNA	Mel3 (melanoma antigens)	CEF	12 of 20 CLOSED
43	A phase I/II trial of polyHER2neu-a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (i.m.)	Breast cancer	St James's University Hospital, Leeds	Application declined	Plasmid	HER-2 epitopes	*E. coli*	Application Declined
44	Treatment of leukaemic relapse after allogenic stem cell transplantation by HSV-tk transduced donor lymphocyte transfusions	Chronic myeloid leukaemia	Hammersmith Hospital, London	10–00	Retrovirus	HSV-tk	AM12	0 of 10-20
45	Phase I clinical gene therapy protocol for X-SCID	X-SCID	Institute of Child Health, London	01–01	Retrovirus	Common gamma chain	PG13	11 of 20 CLOSED
46	Phase I gene therapy protocol for X-CGD	X-CGD	Institute of Child Health, London; Royal Free Hospital, London	12–00	Retrovirus	Gp91-phox	HEK293	3 of 5

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
47	A phase I, randomised, double-blind, placebo-controlled, escalating dose, multicentre study of Ad2/ hypoxia inducible factor gene transfer administered by intramyocardial injection during coronary artery bypass grafting surgery in patients with incomplete revascularisation	Coronary artery disease	John Radcliffe Hospital, Oxford; King's College Hospital, London	12–00	Adenovirus	HIF-1a/VP16	HEK293	4 UK patients CLOSED
48	A randomised phase I trial of intravenous CI-1042 with or without entanercept in patients with metastatic carcinoma	Metastatic carcinoma	Hammersmith Hospital, London	12–00	Adenovirus	p53	HEK293	Application withdrawn
49	A phase I/II study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	Metastatic melanoma	CRC Institute for Cancer Studies, Birmingham	02–01	Plasmid complexed with peptide	MART-1 gp-100	*E. coli*	Trial never opened CLOSED
50	A Phase II trial of preoperative intratumoural injection with HSV1716 in patients with resectable squamous cell tumours of the head and neck	Head and neck cancer	Southern General Hospital, Glasgow	05–01	HSV	ICP34.5 deleted	BHK-21/C13	20 of 20 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
51	A multinational, multicenter, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of Ad5FGF-4 in patients with stable angina	Coronary artery disease	Papworth Hospital NHS Trust; Royal Sussex County Hospital; Royal Infirmary of Edinburgh; Hammersmith Hospital, London; King's College Hospital, London; Royal Free Hospital, London; St Thomas' Hospital, London; The London Chest Hospital; Wythenshawe Hospital, Manchester; Nottingham City Hospital; University Hospital Wales, Cardiff; Queen Elizabeth Hospital, Birmingham (to be confirmed)	05–01	Adenovirus	FGF-4	HEK293	17 of 60 in UK 116 of 450 worldwide CLOSED
52	A phase I study to evaluate the safety, tolerability and immunogenicity of two administrations of either plasmid DNA (pSG.HBs) versus placebo or modified vaccinia virus Ankara (MVA.HBs) versus placebo, followed by two boost administrations of MVA.HBs expressing hepatitis B surface antigen in healthy male volunteers	Hepatitis B vaccine trial	TNO BIBRA International, Surrey; University of Oxford; Central Middlesex Hospital	08–01	Vaccinia & plasmid	HBsAg	MVA: Chicken embryo fibroblasts; Plasmid in *E. coli*	18 of 18 CLOSED
53	A pilot study of the safety and immunogenicity of a candidate HIV-1 clade A DNA vaccine, pTHr.HIVA, given by needle injection into the deltoid muscle in HIV-1-seropositive subjects receiving highly active anti-retroviral therapy	HIV	John Radcliffe Hospital, Oxford	05–01	Plasmid	HIV-1 clade A *gag* and 25 HIV-1 *gag, pol, env, nef* CTL epitopes	1 DH1	10 of 10 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
54	A phase II, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of NV1FGF in patients with severe peripheral artery occlusive disease	Peripheral artery occlusive disease	St. George's Hospital, London; Royal Bournemouth Hospital; Leicester Royal Infirmary; Wythenshawe Hospital, Manchester; Freeman Hospital, Newcastle; Royal Free Hospital, London; Bristol Royal Infirmary (CLOSED); Leeds General Infirmary; Southampton General Hospital	08–01	Plasmid	FGF-1	1XAC-1	11 CLOSED
55	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (Phase I intratumoral)	Prostate cancer	Queen Elizabeth Hospital, Birmingham; Freeman Hospital, Newcastle; St James's University Hospital, Leeds	04–01	Adenovirus	Nitro reductase	PER-C6	39 of 44 CLOSED
56	A phase II, multicentre, double-blinded, placebo-controlled, dose-finding study of ZYC101a in the treatment of high-grade squamous intra-epithelial lesions of the uterine cervix	Ano-genital neoplasia III	Hammersmith Hospital, London	11–01	Plasmid	HPV E6 & E7	*E. coli*	0 of 5 CLOSED
57	A phase I, multidose study to evaluate the safety of intramuscular injections of HER-2 DNA in patients with metastatic breast cancer	Breast cancer	Hammersmith Hospital, London	11–01	Plasmid	HER-2	*E. coli*	27 of 27 CLOSED
58	The use of a cDNA vaccine encoding the human MUC1 gene in the treatment of patients with advanced breast cancer – A phase I/II study	Breast cancer	ICRF, Guy's Hospital, London	08–01	Plasmid	MUC-1	*E. coli*	6 of 12-28

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
59	A phase IIa, open-label trial to assess the safety, immunogenicity and efficacy of a prime-boost strategy of TA-CIN administered in association with TA-HPV to patients with high-grade ano-genital intraepithelial neoplasia (AGIN)	Cervical cancer	University of Wales, Cardiff; St. Mary's, Manchester; Addenbrooke's, Cambridge.	07–01	Vaccinia	E6 & E7 HPV	MR-5	29 CLOSED
60	Study of transfection efficacy and safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Breast cancer	Churchill Hospital, Oxford; Queen Elizabeth Hospital, Birmingham	07–01	Retrovirus	P450	TEFLYRD	8 of 8 CLOSED
61	An upward titration study of transfection efficacy and safety of Metxia-OB83 in patients with adenocarcinoma of the prostate	Prostate cancer	The Churchill Hospital, Oxford	08–01	Retrovirus	P450	TEFLYRD	CLOSED
62	First administration to man of an oncolytic herpes virus vector containing a transgene for granulocyte macrophage colony stimulating factor (OncoVex^{GM-CSF}) – A Study of its safety, biodistribution and biological activity.	Melanoma, breast, head & neck, cancer, non-hodgkins lymphoma	Hammersmith Hospital, London; St George's Hospital, London; CR-UK Institute for Cancer Studies, University of Birmingham	11–01	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	30 CLOSED
63	VTP-1/01: a phase I/II trial of intravenous vs. hepatic arterial infusion of an E1A-CR2 deleted adenovirus (VTP-1) in patients with inoperable, metastatic colorectal carcinoma	Metastatic colorectal carcinoma	Hammersmith Hospital, London	Application withdrawn	E1A conserved region 2 deleted & E3B RID gene region deleted	N/A	HEK-293	Application withdrawn
64	A Phase I trial of replication-competent herpes simplex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma	Malignant pleural mesothelioma	University of Glasgow; Beatson Oncology Centre, Glasgow	02–02	HSV HSV1716	ICP34.5 deleted	BHK-21/C13	0 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
65	A Phase I trial of PolyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma patients	Melanoma	St James's Hospital, Leeds	01–02	Plasmid DNA (polyMEL)	Multiple melanoma epitopes	*E. coli*	9 of 12
66	A recombinant vaccinia ankara (MVA)-based vaccine encoding epstein-barr virus target antigens: phase I dose-escalation trial to determine immunogenicity and toxicity in patients with EBV+ malignancy EuraCT: 2004-001931-46	Naso-pharyngeal carcinoma	Queen Elizabeth Hospital, Birmingham; Royal Marsden Hospital, London	02–02	DNA plus MVA	EBV epitopes (EBNA1 and LMP2A)	CEF	2 of 15
67	Percutaneous intramyocardial gene therapy against myocardial ischaemia with phVEGF-A165SR – a double-blind, placebo-controlled study	Coronary artery disease	Wythenshawe Hospital, Manchester	Application pending	Plasmid	VEGF	*E. coli*	Application withdrawn
68	A phase I trial of polyHER2neu – a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of breast cancer	Breast cancer	The Leeds Teaching Hospital NHS Trust, Leeds	01–02; Revalidated 06/06	Plasmid DNA	Poly epitopes of HER-2	*E. coli*	1 of 12-15
69	A phase I/II study of vaccination with a DNA fusion gene containing an epitope of CMV in allograft donors and patients awaiting renal transplantation	CMV infection following transplant	Southampton General Hospital; Royal Free Hospital, London; University College London Hospital	02–02	Plasmid DNA (pcDNA3)	Peptide from pp65 from CMV	*E. coli*	4 of 15 pairs (8 patients)
70	NUMBER NOT ALLOCATED							
71	A Phase I/II prospective study of immuno gene therapy with a liposomally encapsulated replication incompetent Semliki Forest Virus (SFV) vector carrying the human interleukin-12 gene and administered intratumorally in patients with recurrent or progressing glioblastoma multiforme	Glioma	University of Liverpool	Application withdrawn	Replication disabled Semliki Forest Virus, liposome encapsulated	Human IL-2	Baby hamster kidney (BHK)	Trial withdrawn

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
72	Phase I/II study to determine the optimum dose and dosing regimen, then to assess the efficacy of a poly-epitope pharmaccine, involving pSG2.Mel3 and MVA.Mel3, in patients with stage III or stage IV metastatic melanoma	Metastatic melanoma	Christie Hospital, Manchester; Churchill Hospital, Oxford; Western General, Edinburgh; Southampton General Hospital	09–02	DNA and MVA	Multiple melanoma epitopes	CEF	41 of 41 CLOSED to recruitment
73	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	Severe combined immunodeficiency	Great Ormond Street Hospital, London	12–02	Retrovirus (spleen focus forming virus)	Adenosine deaminase	PG13	5 of 5
74	A randomised efficacy trial of herpes simplex virus hsv1716 in recurrent glioblastoma multiforme (EudraCT: 2004-000097-32)	Glioblastoma multiforme	University Hospital Birmingham NHS Trust; Southern General Hospital, Glasgow; Sheffield Teaching Hospitals NHS Foundation Trusts; Brighton & Sussex University Hospitals NHS Trust; Lancashire Teaching Hospitals NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust	07–04	HSV	ICP34.5 deleted	BHK21.c13	11 of 100
75	A Phase I study of NYVAC C in healthy volunteers at low risk of HIV infection (EV01)	HIV-1	Imperial College London	02–03	MVA	HIV-1 Clade C *gag, pol, nef, env,* (NYVAC C)	Chicken embryo fibroblasts	12 of 12 CLOSED
76	A phase I/II study of DNA vaccination with a CEA/pDOM fusion gene in patients with carcinoma expressing CEA EudraCT: 2004-00193221	Carcinoma	Southampton University Hospital NHS Trust; Western General Hospital, Edinburgh; Portsmouth Hospitals NHS Trust; Leeds Teaching Hospitals NHS Trust	02–03	Plasmid DNA (pcDNA3)	CAP-1 peptide from CEA	*E. coli*	21 of 30

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
77	Gene therapy protocol for the evaluation of the safety and efficacy of TroVax in conjunction with chemotherapy in patients with metastatic colorectal cancer	Metastatic colorectal cancer	Christie Hospital, Manchester; Queen Elizabeth Hospital, Birmingham	02–03	MVA	Human oncofoetal antigen 5T4	Chicken embryo fibroblasts	19 of 19 CLOSED to recruitment
78	A phase I clinical gene therapy trial for X-SCID using umbilical cord blood	X-SCID	Institute of Child Health, London	02–03	Retrovirus (Moloney murine leukaemia virus)	Common gamma chain	PG13	0 of 10 CLOSED
79	A pilot study to evaluate the safety, tolerability and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, delivered to HIV-1 sero-positive adults receiving HAART EudraCT: 2006-000484-29	HIV-1	MRC Human Immunology Unit, John Radcliffe Hospital, Oxford	07–03	MVA	HIV-1 clade A *gag, pol, nef and env*	CEF	10 of 20 CLOSED to new recruitment; Extension phase CLOSED
80	Phase I/II study – first administration of dendritic cells transduced with ImmunoVEXTRI-melan to patients with metastatic or inoperable melanoma	Metastatic or inoperable melanoma	St George's Hospital Medical School, London	Application declined	HSV	hTyrosinase, hMART1, hGP100	Vero (*MEVP16/M4 F6A*)	Application declined
81	An open-label study of TroVax given in conjunction with 5-Fluorouracil/ Leukovorin/Oxaliplatin: safety and immunogenicity before, during and after chemotherapy (TV2)	Colorectal cancer	University of Leeds School of Medicine; Hammersmith Hospital, London	05–03	MVA	Human oncofoetal antigen 5T4	CEF	17 of 17 CLOSED to recruitment
82	A phase II trial to evaluate efficacy and safety of intramuscular injections of HER-2 DNA AutovacTM in patients with metastatic or locally advanced breast cancer	Breast cancer	Hammersmith Hospital	07–03	Plasmid	HER-2 with T cell epitopes P2 and P30 derived from tetanus toxin	*E. coli*	Trial withdrawn
83	A Phase I/II safety study of MetXia-OB83 in patients with pancreatic cancer	Pancreatic cancer	Royal Liverpool University Hospital; Hammersmith Hospitals, London	10–03	Retrovirus (Moloney murine leukaemia virus)	cytochrome P450	FLY RD83	31 of 27

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
84	A Phase I study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	Malignant melanoma	Hammersmith Hospital	07–03	Plasmid DNA	MART-1 and gp-100	*E. coli*	27 CLOSED
85	A phase I trial to assess the safety of DNA C, and the safety and immunogenicity of DNA C followed by NYVAC C, in an open, randomised comparison to NYVAC C alone in healthy volunteers at low risk of HIV infection (EV02) EudraCT: 2004-001802-28	HIV-1	Imperial College London, St's Mary's Hospital	10–03	Plasmid pORT1 And MVA	HIV-1 clade C *gag, pol, nef, env*	*E. coli*	15 CLOSED
86	First administration of dendritic cells transduced with ImmunoVEXTri-Melan to patients with metastatic or inoperable melanoma, preliminary assessment of safety, biodistribution and indicators of efficacy	Metastatic or inoperable melanoma	St George's Hospital Medical School, London & CRUK Oncology Unit, Southampton; Southampton University Hospital NHS Trust; Moorfields Eye Clinic at St George's Hospital Medical School; St Lukes Cancer Centre, Royal Surrey County Hospital	10–03	HSV	hTyrosinase, hMART1, hGP100	Vero (MEVP16/M4 F6A)	19 CLOSED for recruitment
87	A Phase II study immunologically evaluating 5T4-MVA (TroVax) in patients undergoing surgical resection of colorectal liver metastases	Metastatic colorectal cancer	Christie Research Centre, Manchester; North Manchester General Hospital	01–04	MVA	Human oncofoetal antigen 5T4	Chicken embryo fibroblasts	20 of 20 CLOSED for recruitment
88	A Cancer Research UK phase I trial of AEG35156/GEM640 (XIAP antisense) administered as a 7-day continuous intravenous infusion in patients with advanced tumours	Advanced tumours	Christie Hospital NHS Trust, Edinburgh Royal Infirmary	12–03	N/A	Antisense DNA to human X-linked inhibitor of apoptosis	*N/A*	11 of 18-46

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
89	A Phase I/II trial of a DNA vaccine with a $PSMA_{27}$/ pDom fusion gene given by intramuscular injection in HLA A2+ patients with prostate carcinomas with or without electroporation	Prostate cancer	Southampton University Hospitals NHS Trust; Royal Marsden Foundation Trust, London	02–04	DNA with and without electroporation	1st domain of Tetanus toxin fragment C, 9 amino acid peptide from PSMA	*E. coli*	30 of 32
90	A controlled, randomised, parallel group, multicentre study of the efficacy and safety of herpes simplex virus-thymidine kinase gene therapy (Cerepro™), with subsequent ganciclovir, for the treatment of patients with operable high-grade glioma EudraCT: 2004-000464-28	Operable primary or recurrent high-grade glioma	Walton Centre for Neurology and Neurosurgery, Liverpool (withdrawn); Queen's Medical Centre, Nottingham; Addenbrooke's NHS Trust, Cambridge; Queen Elizabeth Hospital, Birmingham	04–04	Adenovirus type 5, E1 and E3 deleted	Herpes simplex virus-thymidine kinase gene (HSV-tk)	HEK293	5 Target: 250 world-wide
91	Double-blind, randomised, placebo-controlled, parallel-group and dose-finding, multicentre, safety and efficacy study with intramuscular injections of NV1FGF in subjects with intermittent claudication	Peripheral artery occlusive disease in patients with intermittent claudication	Royal Bournemouth Hospital; Gloucestershire Hospitals NHS Foundation Trust, Cheltenham; Newcastle Upon Tyne Hospitals NHS Trust	03–04	Plasmid	FGF-1	*E.coli* XAC-1	0 118 subjects worldwide CLOSED for recruitment
92	A randomised, phase II trial of PANVAC vaccination in the adjuvant treatment of stage II colorectal cancer EudraCT: 2004-001734-16	Colorectal cancer	Oxford Radcliffe Hospitals NHS Trust & CRUK Medical Oncology Unit, Oxford	06–04	Vaccinia and fowlpox virus	Carcino-embryonic antigen, Mucin-1, B7-1, ICAM-1 and LFA-3		0 of 40 CLOSED

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
93	An open, randomised, parallel-group study to evaluate the safety, tolerability and immunogenicity of the GW825780 DNA immunotherapeutic when delivered using the PowderJect ND5.5 device to healthy adult volunteer subjects EudraCT: 2004-000251-41	HIV	Addenbrooke's Hospital, Cambridge; Chiltern International, Slough	06–04	Plasmid on gold particles	Reverse transcriptase, *nef*, *gag* of HIV-1	*E. coli* DH1	37 CLOSED for recruitment
94	A Phase II exploratory study of the efficacy and safety of OncoVEX GM-CSF in combination with Arimidex in the neoadjuvant treatment of breast cancer in post-menopausal women with oestrogen receptor positive tumours EudraCT: 2004 –01938-16	Breast cancer	Hammersmith Hospitals NHS Trust	Application declined	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	Declined
95	Safety and immunology evaluation of TroVax produced by the Baxter synthetic route in patients with stage IV colorectal cancer EudraCT: 2004-002251-13	Colorectal cancer	Christie Hospital NHS Trust, Manchester; The Leeds Teaching Hospitals NHS Trust	11/04	MVA	Human oncofoetal antigen 5T4	Chicken embryo cells	Application withdrawn
96	A phase I study of adoptive transfer of autologous tumour antigen-specific T cells with pre-conditioning chemotherapy and intravenous IL2 in patients with advanced cea positive tumours EudraCT: 2005-004085-16	CEA positive malignancies	Christie Hospital NHS Trust, Manchester	11–04	Retrovirus	MFE23 specific for carcino-embryonic antigen; CD3z	Murine PG13	0 of 15
97	A multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy of BIOBYPASS (ADGVVEGF121.10NH) delivered by NOGATM -Guided/myostar catheter in no option patients with class II-IV stable angina EudraCT: 2004-001250-91	Stable angina	King's College Hospital; Barts and the London NHS Trust	11–04	Adenovirus type 5	VEGF	Human embryonic retinoblasts (PER.C6)	6 of 129 CLOSED for recruitment No UK patients recruited

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
98	A pilot study of lentivirus transduced acute myeloid leukaemia (AML) blasts expressing B7.1 (CD80) and IL-2 for the induction of graft verses leukaemia (GVL) effect in poor prognosis, relapsed AML EudraCT: 2005-000806-29	Acute myeloid leukaemia	King's College Hospital, London	11–04 Full approval Dec 07	Lentivirus (HIV-1)	CD80 (B7.1) and IL-2	Human embryonic kidney 293T	0 of 10
99	A Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicentre, dose-selection study of Ad2/hypoxia inducible factor HIF-1a/VP16 in patients with intermittent claudication EudraCT: 2004-002508-13	Peripheral artery disease: intermittent claudication	Ninewells Hospital, Dundee; St George's Hospital Medical School, London; Freeman Hospital, Newcastle (withdrawn); Belfast City Hospital Trust; Ealing Hospital NHS Trust; Hull and East Yorkshire NHS Trust & University of Hull; University Hospital Birmingham Foundation Trust; Hammersmith Hospitals NHS Trust	11–04	Adenovirus (E1 and E4 deleted)	HIF-1a (Hypoxia-Inducible Factor-1)	Human 293 cells	29 of 35
100	A phase II study of NY-ESO-1 ISCOMATRIX® vaccine followed by recombinant fowlpox NY-ESO-1 (rF-NY-ESO-1) or NY-ESO-1 ISCOMATRIX® vaccine alone in patients with high-risk resected NY-ESO-1 positive melanoma and prostate cancer EudraCT: 2004-004991-36	Melanoma or prostate carcinoma	Oxford Radcliffe Hospitals NHS Trust; Southampton University Hospitals NHS Trust; Mount Vernon Hospital	Conditional approval, 03–05; approval 05–05	Recombinant fowlpox virus	NY-ESO-1 tumour specific antigen	Chicken embryo dermal (CED) cells	2 of 40

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
101	An ascending-dose trial of the safety, tolerability and biological effect of intra-arterial injection of the selectively replication-competent herpes simplex virus HSV1716 in patients with unresectable hepatocellular carcinoma EudraCT: 2005-000133-38	Hepatocellular carcinoma	Royal Infirmary of Edinburgh	Declined 04–05	HSV1716	HSV deleted in both copies of RL1 gene	BHK21.c13	Declined
102	A phase I trial of intra-peritoneal Ad-hTR-NTR and CB 1954, an adenovirus-delivered telomerase-directed enzyme-prodrug therapy, in patients with advanced intra-abdominal cancer EudraCT: 2005-003294-24	Intra-abdominal cancer	Beatson Oncology Centre, Western infirmary, Glasgow	Conditional approval, 04–05	Adenovirus (E1/ E3 deleted)	Bacterial nitroreductase gene	Human 293 cells	0 of 8-12
103	A phase I study of adoptive transfer of autologous tumour antigen-specific T cells with pre-conditioning chemotherapy and intravenous IL2 in patients with CD19 positive malignancy	CD19 positive cancer	Christie Research Centre, Manchester	06–05	Retrovirus	Chimeric immune receptor CD19-z cDNA.	Murine PG13	0 of 22
104	Safety, immunology and efficacy evaluation of TroVax in patients with stage IV clear cell renal carcinoma (TV2) EudraCT: 2005-000088-24	Renal carcinoma	Christie Research Centre, Manchester; Institute for cancer studies, Birmingham	Conditional approval, 04 –05	Attenuated vaccinia virus vector MVA	Human oncofoetal antigen 5T4	Chicken embryo cells (CECs)	0 of 10 Application withdrawn
105	An exploratory study of the safety and biological activity of OncoVexGM-CSF in combination with radiotherapy and cisplatin in the treatment of locally advance epithelial cancer of the head and neck EudraCT: 2005-000777-21	Head and neck cancer	Royal Marsden Hospital NHS Foundation Trust, London; Barts and the London NHS Trust	Conditional approval, 04–05; approval 08–05	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	17 of 26

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
106	Phase I/II clinical trial of T cell suicide gene therapy following allogeneic haematopoietic stem cell transplantation EudraCT: 2005-001925-27	To prevent GvHD in children and adults undergoing DLI after bone marrow transplant	Great Ormond Street Hospital NHS Trust; Royal Free Hospital, London	Declined	Retrovirus	HSV-TK (herpes simplex thymidine kinase – splice corrected version)	PG13	Application declined
107	A multicentre, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of BHT-3009 when administered intramuscularly to patients with relapsing remitting multiple sclerosis (Protocol No. BHT-3009-03) EudraCT: 2005-001340-22	Multiple sclerosis	Guy's and St Thomas' NHS Foundation Trust; Royal Hallamshire Hospital, Sheffield; Walton Neurology Centre, Liverpool; Queens Medical Centre, Nottingham; Barking, Havering and Redbridge Hospitals NHS Trust; Royal Victoria Infirmary, Newcastle	06–05	Plasmid DNA	Human myelin basic protein (hMBP)	*E. coli*	4 CLOSED to recruitment in the UK
108	An open-label, international, multicentre, dose-escalating, phase I/II study of SPC2996, an LNA antisense molecule, against Bcl-2 in patients with relapsed or refractory chronic lymphocytic leukaemia EudraCT: 2004-004741-17	Chronic lymphocytic leukaemia	Christie Hospital NHS Trust, Manchester; Barts and the London NHS Trust, London; Leeds Teaching Hospitals NHS Trust; UHL NHS Trust, Leicester; Royal Marsden NHS Foundation Trust	Conditional approval 06–05; approval 08–05	N/A	Antisense DNA binding to mRNA of Bcl-2	N/A	35 of 42 CLOSED
109	A phase I, dose-escalating trial of JX-594 (thymidine kinase-deleted vaccinia virus encoding GM-CSF) administered by intravenous infusion in patients with refractory solid tumours EudraCT: 2005-002015-25	Solid tumours	Radcliffe Infirmary, Oxford	06–05	Replication-selective oncolytic vaccinia virus (TK depleted)	GM-CSF	Vero cells	0 of 20-30

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
110	A Single-arm, open-label phase I study of an injectable replication-incompetent adenoviral vector encoding a factor VII immunoconjugate to induce a cytolytic immune response against the vasculature of carcinoma of the bowel with metastatic lesions to the liver	Liver and colorectal cancer	Hammersmith Hospital, London	Declined	Adenovirus	Factor VII		Declined
111	A phase II, double blind, crossover study to compare the safety and efficacy of 125, 250 and 500 ug/kg Monarsen (EN101) administered to patients with myasthenia gravis EudraCT: 2005–002740–26	Myasthenia gravis	Hope Hospital, Salford; The Walton Centre, Liverpool	09/05	N/A	Antisense oligodeoxy-nucleotide against Acetylcholin-esterase	N/A	10 of 30

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
112	A phase III, randomized, open-label study of docetaxel in combination with CG1940 and CG8711 versus docetaxel and prednisone in taxane-naïve patients with metastatic hormone-refractory prostate cancer with pain EudraCT: 2005-003275-20	Prostate cancer	Royal Marsden Hospital; Cambridge University Hospitals NHS Foundation Trust; Nottingham University Hospitals NHS Trust; Royal Surrey County Hospital, Guildford; East & North Hertfordshire Hospitals NHS Trust; Lancashire Teaching Hospitals NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust; Scunthorpe General Hospital; Christie Hospital NHS Foundation Trust, Manchester; Hammersmith Hospital, London; Clatterbridge Centre for Oncology NHS Foundation Trust	09/05	AAV	Granulocyte macrophage colony stimulating factor (hgGM-CSF)	Human kidney cells	- of 100

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
113	A phase III, randomized, open-label study of CG1940 and CG8711 versus docetaxel and prednisone in patients with metastatic hormone-refractory prostate cancer who are chemotherapy-naïve EudraCT: 2005-002738-36	Prostate cancer	North Glasgow University Hospitals Division, Glasgow; The Leeds Teaching Hospitals NHS Trust; Newcastle Hospitals NHS Trust; East & North Hertfordshire Hospitals NHS Trust; Nottingham City Hospital NHS Trust; Sheffield Teaching Hospitals NHS Trust; Churchill Hospital, Oxford; Hammersmith Hospitals NHS Trust; Cambridge University Hospitals NHS Foundation Trust; Northampton General Hospital NHS Trust; Northern Lincolnshire & Goole Hospitals NHS Trust, Scunthorpe; Conwy & Denbighshire NHS Trust; Greater Glasgow & Clyde, The Beatson WOS Cancer Centre	09/05	AAV	Granulocyte macrophage colony stimulating factor (hgGM-CSF)	Human kidney cells	0 of 50

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
114	A phase II, randomized, double-blind, placebo-controlled, parallel-group, multi-centre study of Ad2/hypoxia inducible factor (HIF)-1a/VP16 administered by intramuscular injection to patients with no or poor option chronic critical limb ischemia EudraCT: 2005-004068-21	Critical limb ischemia	Ninewells Hospital, Dundee	12/05	Adenovirus (E1 and E4 deleted)	HIF-1a (hypoxia-inducible factor-1)	human 293 cells	0 of 90
115	An open-label, dose-escalation study of a self-complementary, adeno-associated viral vector (scAAV2/8-LP1-hFIXCO) for gene therapy of haemophilia B EudraCT: 2005-005711-17	Haemophilia B	Department of Haematology, University College London	Conditional approval 03/06	Recombinant adeno-associated virus (rAAV)	Human FIX gene	293T	0 of 12 from the UK
116	Phase I/II clinical trial of T cell suicide gene therapy following haploidentical stem cell transplantation EuraCT: 2005-001925-27	To prevent GvHD	Great Ormond Street Hospital NHS Trust; Royal Free Hospital, London	06/06	Retrovirus	HSV-TK (herpes simplex thymidine kinase – splice corrected version)	PG13	
117	A Phase I/II feasibility trial to assess the safety, immunological activity and efficacy of TroVax plus interferon-alpha (INF-a) in patients with advanced or metastatic renal cell cancer. EudraCT: 2006-000753-22	Renal cancer	Christie Hospital NHS Trust, Manchester	Conditional approval 04/06; approval 06/06	Vaccinia	Human oncofoetal antigen 5T4	Chicken embryo fibroblasts	11 of 20 CLOSED
118	A Phase I study evaluating the safety and immunogenicity of a new TB vaccine, MVA85A, in healthy volunteers who are infected with HIV EudraCT: 2006–000076–32	Tuberculosis	The Oxford Radcliffe Hospitals NHS Trust; University of Oxford; Great Western Hospital; Swindon & Marlborough NHS Trust; St Mary's Hospital NHS Trust	Conditional approval 04/06; approval 05/06	MVA	Antigen 85A of M. tuberculosis	Chicken embryo fibroblasts	8 of 20

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
119	An open-label, dose-escalation study of an adeno-associated virus vector (AAV2/2-hRPE65p-hRPE65) for gene therapy of severe early onset retinal degeneration EudraCT: 2006-001571-37	Early-onset retinal degeneration	Moorfields Eye Hospital, London	Conditional approval 04/06; full approval 09/06	AAV2	human RPE65	293T	4 of 12
120	A phase I trial of AEG35156 administered by 2-hour intravenous infusions in patients with advanced cancers EudraCT: 2006-001361-42	Advanced cancers	Wythenshawe Hospital & Christie Hospital; South Manchester University Hospitals NHS Trust	Conditional approval 04/06; approval 05/06	N/A	Antisense DNA to human X-linked inhibitor of apoptosis	*N/A*	29 of 30
121	An open-label, phase I study of CGT-A310, a tropism mediated oncolytic adenovirus, in patients with treatment-refractory metastatic tumours (EudraCT: 2006-002097-21)	Metastatic tumours	Barts and The London Hospital	Conditional approval 07/06	Ad5/35	TRAIL and Ad5 E1A	CGT-C905	0 of 30
122	A randomised double blind dose ranging study to assess the safety tolerability and immunogenicity of a monovalent H5 DNA influenza vaccine (A Vietnam/1194/2004) administered by particle mediated epidermal delivery (PMED) to healthy adults (EudraCT – 2006-001501-29)	Avian flu	GDRU (Guy's hospital, London campus)	07/06	Plasmid	Haemagglutinin antigen from influenza strain H5N1	*E. coli*	75 of 75 CLOSED
123	A prospective, randomised, double-blind, placebo-controlled study to assess the efficacy of a trivalent DNA influenza vaccine administered by particle mediated epidermal delivery (PMED) against a controlled influenza virus challenge EudraCT: 2006-001501-92	Influenza	GDRU (Guy's hospital, London campus); Retroscreen Virology Ltd, Queen Mary, University of London; Barts and the London	Conditional approval 07/06; approval 08/06.	Plasmid	Haemagglutinin antigen (HA) from three different influenza virus strains	*E. coli*	105 of 105 CLOSED for recruitment

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
124	An International, randomised, double-blind, placebo controlled, parallel group study to investigate whether TroVax added to first line standard of care therapy prolongs the survival of patients with locally advanced or metastatic clear-cell renal adenocarcinoma (TRIST) EudraCT: 2006-001246-13	Renal cancer	Christie Hospital NHS Trust, Manchester; The Leeds Teaching Hospitals NHS Trust, Leeds; Nottingham University Hospitals NHS Trust; NHS Greater Glasgow & Clyde; Sheffield Teaching Hospitals NHS Foundation Trust; Royal Surrey County Hospital NHS Trust; Clatterbridge Centre for Oncology NHS Foundation Trust; South Tees Hospitals NHS Trust; East & North Herts NHS Trust; The Royal Wolverhampton Hospitals NHS Trust, Beatson WOS Cancer Centre; Swansea NHS Trust, Churchill Hospital, Oxford Radcliffe Hospitals NHS Trust; University Hospitals of Leicester NHS Trust	09/06	Vaccinia	Human oncofoetal antigen 5T4	Chicken embryo fibroblasts	53 of 700 worldwide

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
124A	TRIST-IR – analysis of immune responses in a sub-set of patients enrolled into an international, randomised, double-blind, placebo controlled, parallel-group study to investigate whether TroVax added to first-line standard of care therapy prolongs the survival of patients with locally advanced or metastatic clear-cell renal adenocarcinoma EudraCT No: 2007-002244-19	Sub-study of study124, taking extra blood samples on some patients only	Christie Hospital NHS Trust, Manchester	Conditional approval 10/07; full approval 12/07				

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
125	Restoring dystrophin expression in duchenne muscular dystrophy: a phase I/II clinical trial using antisense oligonucleotides EudraCT: 2006-003833-33	Duchenne muscular dystrophy	Depts of Paediatrics, Imperial College London Hammersmith Hospital Campus & St Mary's Hospital Campus, London; Newcastle Upon Tyne Hospitals NHS Foundation Trust; Dubowitz Neuomuscular Centre, Hammersmith Hospital NHS Trust; Leeds Teaching Hospital NHS Trust; Royal Preston Hospital; Royal Manchester Children's Hospital; Robert Jones Orthopaedic Hospital, Oswestry; Birmingham Heartlands Hospital; Sheffield Children's NHS Foundation Trust; Evelina Children's Hospital, London	09/06	N/A	Antisense oligonucleotide designed to induce exon "skipping" in exon 51 of the DMD gene	N/A	
126	A phase II study of the efficacy, safety and immunogencity of OncoVEX in patients with stage IIIc and stage IV malignant melanoma EudraCT: 2006-003841-17	Malignant melanoma	Southampton University Hospitals; Royal Marsden Hospital, London.	Conditional approval 09/06; approval 11/06	HSV	Human GM-CSF	WHO Vero cell line	45 – 50

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
127	A phase III, randomized, open-label, multicentre study with early stopping rules, testing TG4010 subcutaneous injections at the dose of 108 pfu in combination with chemotherapy treatment verses chemotherapy alone EudraCT: 2005-001015-22	Lung cancer	Guy's and St Thomas' NHS Foundation Trust, London; Clatterbridge Centre for Oncology NHS Foundation Trust	Conditional approval 09/06; approval 01/07	MVA	Human MUC1 antigen and human Interleukin-2	Chicken embryo fibroblasts	0 of 140; withdrawn in UK
128	WT1 TCR gene therapy of leukaemia: A Phase I/II safety and toxicity trial EudraCT: 2006-004950-25	Leukaemia	The Royal Free Hospital; University College London Hospital	Conditional approval 12/06; full approval Dec 07	Retrovirus	T cell receptor specific for Wilms' tumour antigen 1	PG13	0 of 18
129	An ascending-dose trial of the safety, tolerability and biological effect of intra-arterial injection of the selectively replication-competent herpes simplex virus HSV1716 in patients with unresectable hepatocellular carcinoma EurdraCT: 2005-000133-38	Liver cancer	Queen Elizabeth Hospital, Birmingham	Approval 02/07	HSV	N/A	BHK21.c13	0 of 9
130	A phase I study to assess the safety and immunogenicity of new TB vaccine candidates FP85A and MVA85A in healthy adults who have previously been immunized with BCG, using a prime-boost delivery schedule. EurdraCT: 2007-000014-37	Tuberculosis	Churchill Hospital, Oxford	Approval 02/07	MVA and fowlpox	*M. tuberculosis* antigen 85A	Chicken embryo fibroblasts	12 of 36
131	A phase I/II trial to compare the immunogenicity and safety of 3 DNA C prime followed by 1 NYVAC C boost to 2 DNA C prime followed by 2 NYVAC C boost EudraCT: 2006-006 141-13	HIV infection	St Mary's Hospital, London	Approval 02/07	Vaccinia	HIV-1 *gag, pol, nef, env, (gp120)*, NYVAC C	Chicken embryo fibroblasts	3 of 20

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
132	Gene therapy for SCID-X1 using (SIN) gammaretroviral vector EudraCT Number: 2007-000684-16	X-linked SCID	Great Ormond Street Hospital	Conditional approval 05/07	Gammaretrovirus	Human common cytokine receptor gamma chain (γc)	293T	0 of 10
133	A phase I study to assess the safety and immunogenicity of a new candidate malaria vaccine, AdCh63 ME-TRAP, alone and with MVA ME-TRAP, using a prime boost delivery schedule EudraCT: 2006-005966-37	Malaria	Churchill Hospital, Oxford; Northwick Park Hospital, Harrow	Approval 06/07	AdCh63, MVA	ME-TRAP	HEK 293 cells and CEF cells	0 of 32
134	Measurement of human Tcell turnover following vaccination with the tuberculosis vaccine MVA85A EudraCT: 2007-001293-85	Tuberculosis	Churchill Hospital, Oxford	Approval 05/07	MVA	Antigen 85A	Chicken embryo fibroblasts	3 of 12
135	A randomised, double-blind, placebo-controlled study to evaluate the safety and immunogenicity of a candidate HIV-1 vaccine, MVA.RENTA, delivered intradermally by needle injection, alone or in combination with MVA.HIVA, to HIV-1 seropositive adult subjects receiving highly active antiretroviral therapy (HAART) EudraCT: 2007-002865-11	HIV	John Radcliffe Hospital, Oxford	Approval 07/07	MVA	Combination of HIV derives antigens	Chicken embryo fibroblasts	0 of 30
136	Investigation of the safety and feasibility of SERCA gene transfer in the human failing heart using an adeno-associated viral vector EudraCT: 2007-002809-48	Heart disease	Royal Brompton and Harefield NHS Trust, London; Papworth Hospital, Cambridge	Approval 07/07	AAV	Sarco(endo) plasmic reticulum calcium ion adenosine triphosphatase 2a (SERCA2a)	HEK293	0 of 16

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
137	A randomised, open-label, phase II, non-inferiority clinical study between two manufacturing processes for the tuberculosis vaccine MVA85A EudraCT: 2007-001729-92	Tuberculosis	Churchill Hospital, Oxford	Approval 07/07	MVA	Antigen 85A	Chicken embryo fibroblasts	0 – 30
138	A randomised, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 4 administrations of XRP0038/NV1FGF 4mg at 2-week intervals on amputation or any death in critical limb ischemia patients with skin lesions EudraCT: 2006-006277-24	Critical limb ischemia	The Freeman Hospital, Newcastle upon Tyne	Full approval 10/07	Plasmid	FGF1	*E.coli*	
139	A Phase 1, open-label, dose-escalating study of the safety, tolerability and tumour-specific replication of the intravenous administration of green, fluorescent, protein-encoded, genetically engineered, attenuated vaccinia virus GL-ONC1 with real-time imaging in patients with advanced solid organ cancers EudraCT: 2007-004228-18	Advance-stage solid tumours with green fluorescent protein (GFP)	Royal Marsden Hospital, Sutton	Conditional approval 10/07	Attenuated vaccinia virus	GFP	Chicken embryo fibroblasts	0 of 40-60
140	Safety evaluation of a single escalating dose of pGM169/GL67A in the nose and lung of individuals with cystic fibrosis EudraCT: 2007-004050-85	Cystic fibrosis	National Heart & Lung Institute, London (study conducted at the Royal Brompton Hospital)	Approved 10/07	Lipid GL67	CFTR		0 of 27
141	QUASAR V: A multi-centre, randomised, placebo-controlled trial of TroVax vaccination in the adjuvant treatment of stage II and stage III colorectal cancer	Colorectal cancer	School of Medical Sciences, University of Oxford, Radcliffe Infirmary, Oxford	Conditional approval 10/07	MVA	Tumour-associated antigen 5T4	Chicken embryo fibroblasts	0 of 2786

GTAC No.	Protocol NAME	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
142	A phase I study to assess the safety and imunogenicity of a new candidate malaria vaccine, AdCh63 AMA1 EudraCT 2007-004567-21	Malaria	Churchill Hospital, Oxford	No decision pending further info 10/07	AdCh63,	AMA1	HEK293	0 of 24
143	A Phase I study to assess the safety and immunogenicity of a new influenza vaccine candidate MVA-NP+M1 in healthy adults. EudraCT: 2007-003970-24	Influenza	Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford	approval Dec 07	MVA	H3N2	Chicken embroyo fibroblasts	0 of 24
144	A Phase I study to assess the safety and immunogenicity of new Hepatitis C virus vaccine candidates AdCh3NSmut and Ad6NSmut EudraCT: 2007-004259-12	Hepatitis C	Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford	Conditional approval Dec 07	Ad6 AdCh3	Multiple hepatitis antigens	PER.C6	0 of 36
145	A randomised, open-label, phase II, immunogenicity and exploratory efficacy evaluation of therapeutic immunisation +/- IL-2,GM-CSF and growth hormone in HIV-1 infected subjects receiving highly active anti-retrovial therapy (HAART) EuraCT: 2006-006212-30	HIV-1	Chelsea and Westminster Hospital, London	Conditional approval Dec 07	Plasmid	Multiple HIV antigens	*E.coli*	0 of 30

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The GTAC Secretariat may be contacted at:

Department of Health
Area 603, Wellington House
133-155 Waterloo Road
London SE1 8UG

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